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Influence of Insulin-Like Growth Factor 1 Gene Expression in Women with Breast Cancer: A Systematic Review

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Abstract

Background: Breast cancer, the leading cause of cancer death among women worldwide, one of the major risk factors for breast cancer is genetic changes. Changes in the expression levels of the insulin-like growth factor 1 (*IGF-1)* gene have been associated with increased risk and aggressiveness of breast cancer. The *IGF-1* gene encodes the IGF-1 peptide that is present in most human tissues, as in the normal and neoplastic mammary gland. Here, we conducted a systematic review to investigate the influence of *IGF-1* gene expression levels in women with breast cancer.

Methods: PubMed, Scopus, and Web of Science databases were searched for relevant studies published between February 2 and May 15, 2019, using inclusion and exclusion criteria in accordance with PRISMA guidelines. We analyzed the studies to find association between *IGF-1*gene expression and breast cancer.

Results: A growing number of studies in women with breast cancer support, with controversial results, the influence of *IGF-1* gene expression levels on clinical-pathological factors, disease-free survival, overall survival, and resistance to tamoxifen.

Conclusions: Therefore, the elucidation of *IGF-1* gene expression patterns through further studies may enable the characterization of women at high risk for breast cancer, as well as the development of effective prognostic and therapeutic strategies.

Background

Cancer incidence and mortality are rapidly growing worldwide, representing a serious global health problem [1]. Breast cancer is the most frequently diagnosed malignant neoplasm in the majority of countries and is the leading cause of cancer death among women [2]. For the year 2018, approximately 2.1 million new cases of breast cancer were estimated to occur worldwide [3]. Breast cancer is a complex disease of unknown and multifactorial etiology, in which one of the main risk factors is genetic alteration [4, 5]. Thus, genetic mutations of breast cancer (BRCA) 1 and 2 genes are related to the increased risk of hereditary breast and ovarian cancer over time [6], however, the participation of genes in breast cancer has not yet been fully elucidated [4, 5]. Thus, changes in expression levels of the insulin-like growth factor 1 [*IGF-1*] gene have been evaluated in breast cancer, however, there is a need for further elucidation of the association between changes in *IGF-1* levels and increase in the risk, survival, and disease progression of breast cancer [7, 8].

The IGF system consists of two peptidic hormones (IGF-1 and IGF-2), two cell surface receptors (IGF-1R and IGF-2R), and at least six IGF-binding proteins [IGFBP 1–6] that control normal growth and differentiation in most tissues [9, 10]. The effects of free IGF-1 protein, which represent about 1% of the circulating proteins, are mediated by IGF-1R [11]. The binding of IGF-1 to the IGF-1R receptor triggers two large signaling cascades that stimulate proliferation, protect against apoptosis, and promote cell differentiation [12]. IGF-1 is a single chain polypeptide that belongs to the family of peptidic hormones and is found in most human tissues, such as normal and malignant mammary glands. It is expressed

mainly by the stroma, and rarely by the epithelial cells [13, 14]. In combination with growth hormone, insulin, and sex hormones, IGF-1 acts as a crucial regulator of cell growth, differentiation, and apoptosis, as it has striking mitogenic and antiapoptotic activities in cancer cells, acting synergistically with estrogen to promote tumor growth [15, 12, 16]. The *IGF-1* gene is located on chromosome 12, the q22-q24 band of the human genome, contains six exons and five introns and is 100 kilobases long [17, 18, 19]. As the expression of the *IGF-1* gene is controlled by transcriptional and post-translational modifications, several IGF-1 peptides may result from the use of different promoters, alternative splicing, proteolytic processing, and glycosylation events [20]. Epidemiological and experimental evidence attempted to clarify the role of the IGF-1 axis in human breast cancer and showed controversial results. While some studies indicated that increased levels of *IGF-1* gene expression are associated with a better prognosis in breast cancer [21], other studies have suggested that increased levels of *IGF-1* gene expression could be associated with increased cell proliferation in breast cancer [22, 23]. Thus, altered levels of *IGF-1* gene expression may be related to better prognosis or unfavorable outcomes and greater aggressiveness in breast cancer [21, 22]. However, there is a scarcity of studies on this subject in women with breast cancer. This motivated us to detail, in a systematic review, the available studies in the databases to investigate the influence of *IGF-1* gene expression levels in women with breast cancer.

Methods

Search strategy

The research was carried out using the PubMed, Scopus, and Web of Science databases. Searches were conducted between February 2 and May 15, 2019. The search strategy included the crossing of the following descriptors: “breast cancer” OR “breast neoplasm” AND “IGF-1” AND “gene”; “breast cancer” OR “breast neoplasm” AND “IGF-1” AND “expression”; “breast cancer” OR “breast neoplasm” AND “IGF-1” AND “mRNA”; “breast cancer” OR “breast neoplasm” AND “IGF-1” AND “gene” AND “expression”.

Study Selection And Eligibility Criteria

A collection of eligibility criteria was used to select articles from the literature. Inclusion criteria were studies published between 2009 and 2019, English language publications, and human studies addressing the gene expression of *IGF-1* in breast cancer. Exclusion criteria were duplicate articles, articles with only abstracts available, literature reviews, editorials, letters to the editor, conference proceedings, and articles related to breast cancer and *IGF-1* that did not quantitatively analyze levels of gene expression.

Data Extraction And Quality Assessment

All identified studies were independently reviewed by two authors for the relevance of the inclusion/exclusion criteria. After a primary examination, all the complete studies retrieved were subjected

to a more detailed evaluation, and compared and verified to ensure equivalence in the selection and analysis of articles. The selection process of the studies was mapped according to the preferred reporting items for systematic reviews and meta-analyzes (PRISMA) guidelines [24].

Results

A total of 2,370 studies were identified through PubMed databases (n = 749), Scopus (n = 330), and Web of Science (n = 1,291). After selecting and applying the inclusion and exclusion criteria, 5 articles were included in the present systematic review, according to the flow chart detailing the process of identification, selection, eligibility, and final inclusion of the studies (Fig. 1). The description of the selected studies is shown in Table 1. (Table 1.)

Table 1
Description of the selected studies.

Author	Type of Study	Characteristic Population	Sample Size	Conclusion
Mu et al. [25]	Cohort	Italian women	204 cases of breast cancer	High levels of *IGF-1* mRNA expression were associated with small tumors, earlier stages of the disease, low grade tumors, ER or PR positive tumors, and a better prognosis.
Mu et al. [21]	Cohort	Italian women	204 cases of breast cancer	High levels of *IGF-1* mRNA expression were associated with the luminal A and normal-like subtype, with less aggressive tumors and a better prognosis.
Chong et al. [26]	Cohort	English women	132 cases of breast cancer	*IGF-1* mRNA levels did not correlate with clinicopathological factors. However, increased levels of *IGF-1* mRNA expression were associated with higher DFS.
Raval and Trivedi. [7]	Cohort	Indian women	106 cases of breast cancer	Significantly lower levels of *IGF-1* mRNA expression were observed in breast tumors regardless of age, menopausal status, tumor size, lymph node status and histologic grade. There were no associations with OS and DFS.
Christodoulou et al. [27]	Cohort	Greek women	227 cases of breast cancer	High levels of *IGF-1* mRNA expression were associated with older age and absence of bone metastases. Already decreased levels of expression were associated with histological grade III and metastases.
Chong et al. [28]	Cohort	English women	92 cases of breast cancer	High levels of *IGF-1* mRNA expression were associated with delay in developing resistance to tamoxifen. Decreased levels of *IGF-1* mRNA expression were associated with tamoxifen-resistant tumors.

ER: estrogen receptor; PR: progesterone receptor; DFS: disease-free survival; OS: overall survival.

The association between *IGF-1* mRNA expression levels in tumor tissues of women with breast cancer and the characteristics of the disease was examined by Mu et al. [25]. A significant association was found between increased levels of IGF-1 mRNA expression and small tumors (< 2 cm), earlier stages of disease (stage 1), low grade tumors (grade 1 and 2), and tumors estrogen receptor (ER) or progesterone receptor (PR) positive. Survival analysis showed that women with high *IGF-1* mRNA expression had a lower risk of disease recurrence and death compared to those with low expression.

In another study, Mu et al. [21] evaluated levels of *IGF-1* mRNA expression in tumor tissues of women with breast cancer. Results showed that increased levels of *IGF-1* mRNA expression were associated with

the luminal subtype A, normal-like, and less aggressive tumors (ER positive, low grade, node negative tumors). However, decreased levels of *IGF-1* mRNA expression were associated with the basal, Human epidermal growth factor receptor 2 (HER2), and luminal B subtypes. Thus, the results of their studies showed an inverse association between *IGF-1* mRNA levels and the prognosis of the disease.

Chong et al. [26] analyzed the relationship between *IGF-1* mRNA expression levels in breast tumors and adjacent normal tissues (TNAs), and the clinicopathological and prognostic factors of women with breast cancer. No correlation was observed in tumor tissue and TNAs between *IGF-1* mRNA expression levels and clinicopathological factors, such as histological grade, lymph node status, and tumor size. However, increased levels of *IGF-1* mRNA expression in tumor tissue and TNAs were associated with increased disease free survival (DFS) while lower levels of *IGF-1* mRNA were associated with shorter DFS. A similar pattern of association between IGF-1 mRNA and DFS was observed in ER-positive women. However, patients who developed local recurrence or metastasis had lower levels of *IGF-1* mRNA in tumor tissue and TNAs compared to those who remained disease-free.

Raval and Trivedi [7] studied levels of *IGF-1* mRNA expression in breast tumors and adjunctive normal tissues (TNAs) of women undergoing mastectomy for breast cancer treatment. Significantly lower levels of *IGF-1* mRNA expression were observed in the breast tumors, regardless of age, menopausal status, tumor size, lymph node status and histological stage when compared to those in the TNAs. On the other hand, in this study, the low expression of *IGF-1* mRNA was associated with stages II, III and IV breast tumors without lymphatic permeation. Thus, a significant inverse correlation was observed between stage, histological type, and levels of *IGF-1* mRNA expression. Although low levels of *IGF-1* mRNA expression were observed in patients who developed local recurrence/metastasis and had shorter disease free survival, significant association was not observed with respect to overall survival (OS) and DFS when breast tumors and TNAs were compared.

Christodoulou et al. [27] analyzed the in-tumor expression of *IGF-1* mRNA in patients with trastuzumab-treated HER2-positive metastatic breast cancer and showed that *IGF-1* mRNA expression levels were higher in patients over the age of 50 years at the time of the initial diagnosis and absence of bone metastases. In contrast, decreased levels of *IGF-1* mRNA expression were associated with histological grade III, distal and mainly visceral metastases.

Chong et al. [28] evaluated the levels of *IGF-1* mRNA expression in ER-positive tumors in women treated with tamoxifen. Tumors that showed high levels of *IGF-1* mRNA expression were associated with a significantly longer time to develop resistance to tamoxifen. Tumors resistant to tamoxifen had significantly lower levels of *IGF-1* mRNA expression when compared to tumors sensitive to tamoxifen.

Discussion

This systematic review was conducted with the prospect of investigating the potential influence of *IGF-1* gene expression levels in women with breast cancer. The studies evaluated have shown controversial results related to the levels of *IGF-1* gene expression in women with breast cancer. Mu et al. [25] showed

that elevated *IGF-1* mRNA expression was associated with indicators of good prognosis, including small tumors, more early stages of the disease, low-grade, ER or PR positive tumors, and lower risk of disease recurrence and death. These results agree with previous studies that showed that elevated levels of *IGF-1* mRNA were associated with better prognosis of the disease [29, 30]. In the early stage of breast cancer, there are more number of stromal cells compared to those in the more advanced stage. As stromal cells are the main source of *IGF-1*, this is in agreement with an association between the elevated expression of *IGF-1* mRNA and the earliest stages of the disease [31]. Mu et al. [25] suggested that high-grade tumors that invade adjacent tissues or spread to distant organs may become less dependent on *IGF-1* regulation and that small and low-grade tumorrespond well to *IGF-1* signals. In another study, Mu et al. [21] showed that increased levels of *IGF-1* mRNA expression were associated with luminal A and normal-like subtypes while decreased levels of *IGF-1* mRNA expression were associated with luminal B, HER2 hyperexpressed and triple-negative subtypes [poorly differentiated tumors]. These results may be justified by the fact that high levels of *IGF-1* are suspected to occur only in well-differentiated tumor cells and decreased expression of *IGF-1* occur in poorly differentiated tumor cells [31]. The association of increased levels of *IGF-1* mRNA expression with less aggressive tumors and better prognosis [21] appears to be in agreement with findings from previous studies [25, 30], suggesting that it is possible that only less aggressive tumors respond well to *IGF-1* signals [25]. The finding of an inverse association between *IGF-1* mRNA and better prognosis of the disease is not surprising, since the IGF system is closely linked to estrogen receptor signaling and these tumors are typically slower and well differentiated [21].

In a study by Chong et al. [26], even though correlation was not observed between *IGF-1* mRNA expression levels and pathological clinical factors such as histological grade, lymph node status and tumor size [26], increased levels of *IGF-1* mRNA expression in tumor tissue and TNAs were found to be associated with higher DFS and this was statistically independent of other pathological clinical features [26]. These findings agree with previous studies where high *IGF-1* mRNA expression was established as an independent predictor of higher DFS and OS [29] and [30], suggesting that the IGF-1 gene may increase cell differentiation in certain types of cancer and this would be associated with less aggressive cancers and consequently with better prognosis [32, 33].

Raval and Trivedi [7] showed significantly lower levels of *IGF-1* mRNA expression in women's breast tumors compared to those in TNAs. These findings are in agreement with two other studies [34, 35] suggesting the existence of a paracrine relation within the local environment of the cancerous mammary tissue, where the expression may differ according to the type of cell present within the tissues, and the greater expression of IGF-1 in TNAs would stimulate cell proliferation and inhibit apoptosis, causing levels to be high in TNAs and lowin breast tumors [7]. The non-association of *IGF-1* mRNA levels with OS and DFS when compared to breast tumors and TNAs [7] contradicts previous studies that have shown that a high expression of the *IGF-1* gene in breast cancer tissues is correlated witha more favorable DFS and OS [30] and that increased levels of *IGF-1* in tumor tissue and TNAs are associated with higher DFS while the decreased levels in tumor tissue and TNAs are correlated to lower DFS [26].

The findings of Christodoulou et al. [27] in women with HER2-positive breast cancer treated with trastuzumab showed elevated levels of *IGF-1* mRNA expression in women older than 50 years at the time of diagnosis and absence of bone metastases. On the contrary, decreased levels of *IGF-1* mRNA expression were found in patients with histological grade III and visceral distal metastases, which may be justified by the fact that IGF-1 could be involved in the mechanism of resistance to treatment with trastuzumab [36, 37] suggesting that cross-communication of IGF-1 / HER2 may occur via autocrine and/or paracrine signaling in breast cancer [38, 39, 40]. Theoretically, IGF-1 should stimulate breast cancer cells via IGF-1R, which would lead to anti-apoptotic effects and promote resistance to tamoxifen treatment [28]. However, the study by Chong et al. [28] has shown that higher levels of *IGF-1* mRNA expression are associated with lower tamoxifen resistance by breast cancer. Some studies have shown that resistance to tamoxifen may be due to altered downstream cellular pathways involving IGF-1 [41, 42, 43]. Nevertheless, the results are conflicting, since other studies have shown that *IGF-1* expression and activity are important in maintaining a tamoxifen-resistant phenotype [41, 44], while other authors have shown a reduction in IGF- 1 in cell lines resistant to tamoxifen [45]. However, patients with tamoxifen-sensitive breast cancer had not yet used the drug at the time of the biopsy and were under estrogenic stimulation, which could explain the higher levels of *IGF-1* mRNA in these patients, unlike breast cancers resistant to tamoxifen that become independent of estrogen stimulation, and as IGF-1 tends to correlate with estrogen, this may justify low levels of *IGF-1* mRNA in these tumors [28]. A probable explanation for conflicting results found among the authors is due to the limitations of the studies evaluated, especially lack of standardization in the methodology, where different protocols of gene expression analysis were used, and heterogeneous samples with relatively small sample numbers and with different ethnicities.

Conclusion

This systematic review provides evidence that increased or decreased levels of *IGF-1* gene expression may be associated with clinicopathological aspects of breast cancer, DFS, OS, and resistance to tamoxifen in women with breast cancer. However, there is a shortage of studies on the subject, mainly with larger samples, in Latin American women with recurrence of breast cancer. Therefore, the elucidation of *IGF-1* gene expression patterns through further studies may allow the characterization of women at high risk forbreast cancer, as well as the development of strategies for prognosis and effective treatment, allowing better survival and reduction of progression of the disease.

Abbreviations

BRCA: breast cancer; DFS: disease-free survival; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; *IGF*-1: insulin-like growth factor 1; IGF-1 and IGF-2: two peptidic hormones; IGF-1R and IGF-2R: two cell surface receptors; IGFBP 1–6: six IGF-binding proteins; OS: overall survival; PR: progesterone receptor; PRISMA: preferred reporting items for systematic reviews and meta-analyzes; TNAs: adjacent normal tissues

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Availability of data and materials

All data generated in this analysis are available from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

DRCS, MCBO, FMN, LCCV, and ROP made substantial contributions to conception and acquisition of data. PVLC, SFVV, ARS, JLV, and CBT, participated in drafting the manuscript. EBS, RJVV, ALPS, EAV, MAM, ACC and EGC made substantial contributions to acquisition of data. BBS and LHG, supervised and revised the manuscript critically. All authors have read and approved the manuscript.

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Figures

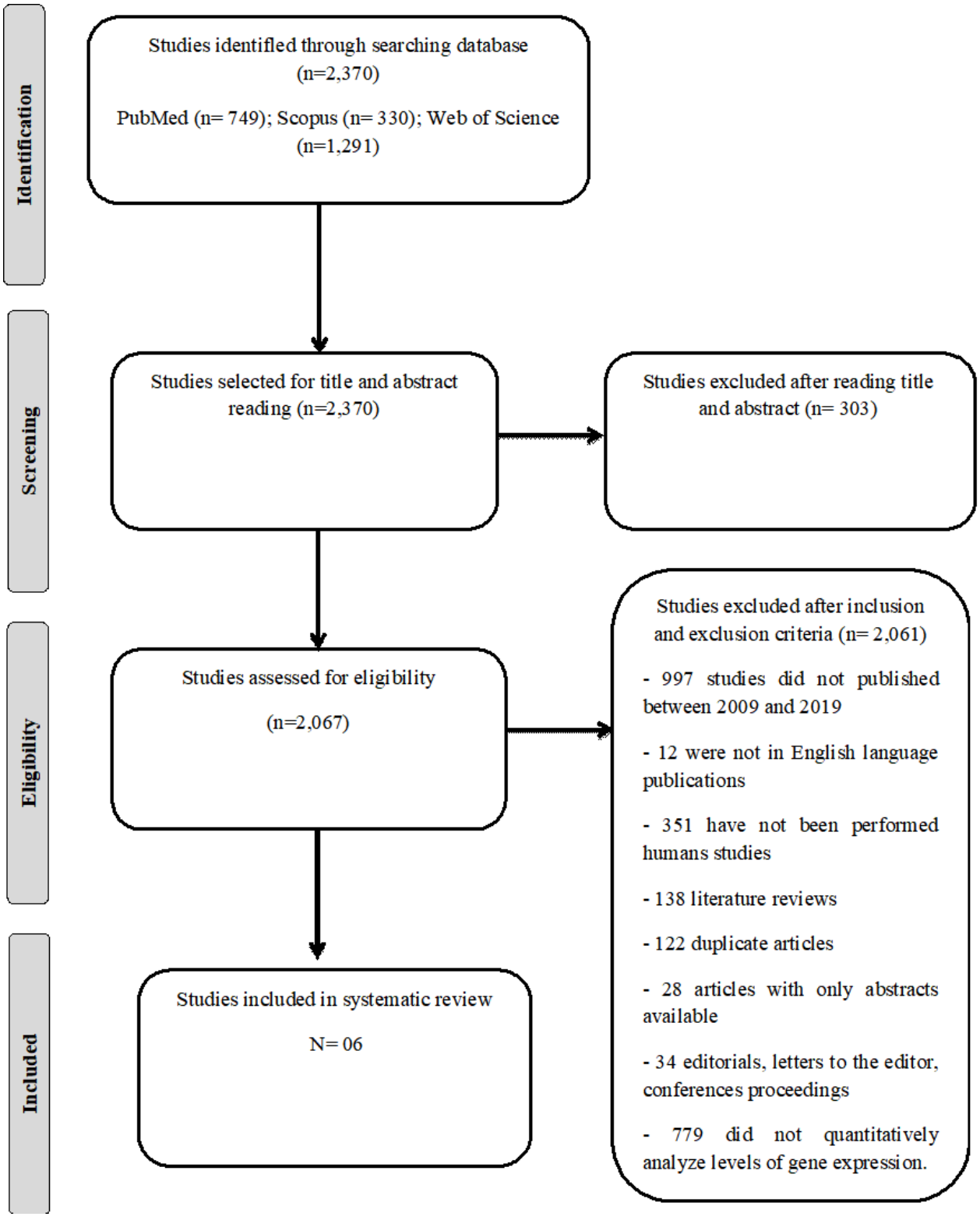

Figure 1

Flow chart detailing the process of identification, selection, eligibility, and final inclusion of the studies.

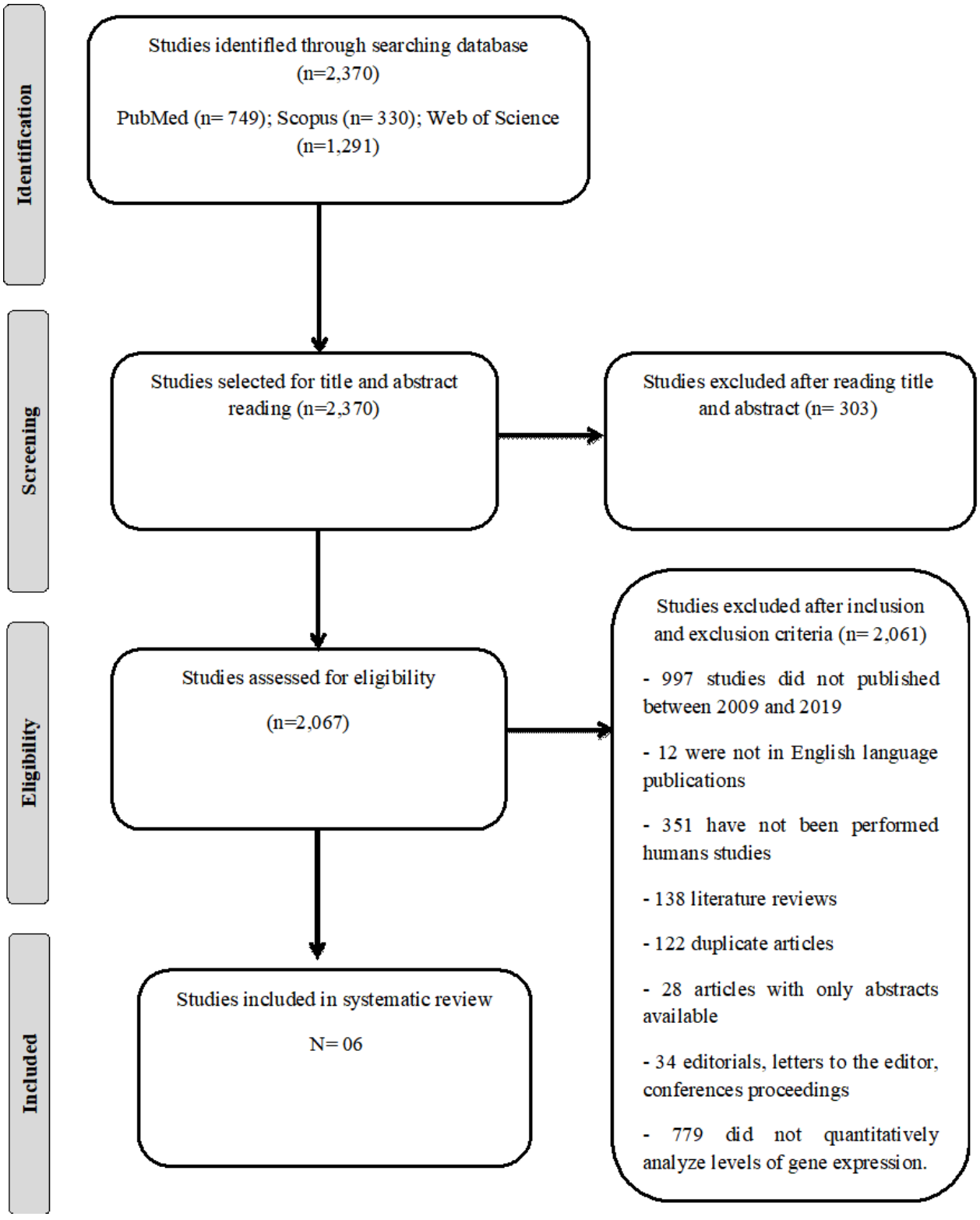

Figure 1

Flow chart detailing the process of identification, selection, eligibility, and final inclusion of the studies.

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