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Evaluation of the Effect of Mesenchymal Stem Cells on Breast Cancer Migration and Metastasis: A Systematic Review and Meta-analysis

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ABSTRACT

Background and aim: Insufficient evidence in the field of the effect of MSCs on the migration of breast cancer cells caused the present study to be conducted with the consensus of the findings and to perform a meta-analysis to evaluate the effect of mesenchymal stem cells on breast cancer migration and metastasis.

Material and methods: In the present systematic review and meta-analysis, information about mesenchymal stem cells in breast cancer patients in all articles published until the end of July 2023 through searching in databases PubMed, Scopus, Science Direct, ISI, Web of Knowledge, Elsevier, Wiley, and Embase and Google Scholar search engine were extracted using keywords and their combinations by two trained researchers independently. Data analysis was done using the fixed effects model in the meta-analysis by STATA (version 17); a p-value less than 0.05 was considered significant.

Results: Thirteen in-vitro and in-vivo studies were included in the meta-analysis process. The risk ratio of incidence of metastasis after MSCs administration was 7.37 (RR, 95% CI: 7.23, 7.53; I2 =99.86% (p=0.00), very high heterogeneity); human-MSCs from different sources appear to increase the migratory activity of MDA-MB-231 cells and MCF-7 cells compared to control group($p<0.01$).

Conclusions: Meta-analysis showed that MSCs are significantly effective in increasing the migration of breast cancer cells and metastasis. Therefore, MSCs can be a promising option for treating breast cancer metastases.

1. Introduction

Breast cancer is considered one of the most severe cancers of women worldwide. Like other cancers, this cancer is affected by various genetic and environmental factors. The set of these factors will cause this cancer.[1] Aging is one of the most important factors in the occurrence of breast cancer.[2] After the initial diagnosis of cancer, choosing the appropriate treatment method depends on various factors such as the rate of cancer progression, tumor size, tumor location, metastasis, and the patient's physical condition.[3] Treatment methods such as surgery, chemotherapy, and radiation therapy are the most common types of treatment.[4] Today, new cancer treatment methods, such as stem cells, have provided a promising option in the path of cancer treatment.[5, 6] Among the types of stem cells, mesenchymal stem cells (MSCs) are attracting the attention of researchers due to their features, such as the presence of abundant sources of extraction, the possibility of large-scale cultivation, the ability to differentiate into different types of cells, and the secretion of various factors.[7]

MSCs can modulate the immune system.[8] In laboratory conditions, they can interact and regulate the function of the most effective cells in the primary and acquired response processes.[9] Another application of MSCs is using these cells to repair damaged tissues.[10] Because of their ability to migrate, MSCs can migrate to damaged areas due to the possibility of differentiating into some cells of the damaged area and the ability to secrete chemokines, cytokines, and growth factors that help tissue regeneration, causing tissue repair and recovery.[11] MSCs, in response to injury signals, can migrate from their host into the peripheral circulation, pass through the vessel wall, and reach target tissues.[12] Today, studies have shown the beneficial effects of MSCs-based therapy for healing various injuries,[13] neurological disorders,[14, 15] cardiac ischemia,[16, 17] diabetes,[18, 19] and bone and cartilage diseases.[20] However, the therapeutic potential of MSCs in cancer is still debated. The ability of MSCs to interact with the microenvironment of cancer cells has led

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to the use of these cells in cancer studies.[21, 22] Some of the conducted experiments show the effect of MSCs in preventing tumor initiation and progression and inhibiting cancer cell proliferation.[23] Also, MSCs may be effective in all stages of carcinogenesis, such as the creation of cancer stem cells, tumor growth, epithelial to mesenchymal transformation, and angiogenesis, and lead to tumor progression and metastasis.[24] Insufficient evidence of the effect of MSCs on the migration of breast cancer cells caused the present study to be conducted with the consensus of the findings and to perform a meta-analysis to evaluate the effect of mesenchymal stem cells on breast cancer migration and metastasis.

2. Material and methods

Search strategy

In the present study, in order to obtain scientific documents and evidence related to MSCs on the migration of breast cancer cells, articles published in international databases such as PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI, Elsevier, Embase, and Google Scholar search engine were used. The search process until July 2023 in the PubMed database was done using MeSH keywords: (((((((("Neoplasms"[Mesh]) OR "Neoplasms/therapy"[Mesh]) OR "Breast Neoplasms"[Mesh]) OR "Breast Neoplasms/therapy"[Mesh]) AND ("Stem Cells"[Mesh] OR "Mesenchymal Stem Cells"[Mesh]) AND "Cell Movement"[Mesh]) OR "MDA-MB-231 Cells"[Mesh]) OR "MCF-7 Cells"[Mesh]) AND "Neoplasm Metastasis"[Mesh]; and search process in other database was done until July 2023 using English keywords: neoplasm, cancer, therapy, treatment, breast neoplasm, breast cancer, stem cells, mesenchymal stem cells, migration, MDA-MB-231 Cells, MCF-7 Cells, neoplasm metastasis, metastasis. In addition, the reference list of the obtained articles was checked to identify the articles that were not obtained using the above methods. Databases were searched with high sensitivity. Two researchers searched independently to avoid bias.

Study selection criteria

Inclusion criteria

Use of the PECOS (patient/population, exposure, comparison, outcome, and study design) strategy to construct the research question is specified in Table 1; in-vitro studies, availability of the full text of the article; and published in English. Studies with incomplete results, case studies, case reports, and review articles were excluded.

Table1. PECO strategy.

PECO Strategy	Description
P	Population: Breast Cancer Cells
E	Exposure: Mesenchymal stem cells
C	Comparison: Control group
O	Outcome: Effects of MSCs on MDA-MB-231 and MCF-7 cells, breast cancer migration, breast cancer metastasis
S	Study design: In-vitro and in-vivo studies

Data collection

A checklist was designed based on the objectives, and information from the selected articles was entered into the checklist (Tables 2 and 3).

Risk assessment

National Toxicology Program's Office of Health Assessment and Translation (OHAT) risk of bias rating tool approach to evaluating the risk of bias in human and animal studies to facilitate consideration of bias across elements and evidence streams with common terms and categories. Potential sources of bias are assessed with a set of 10 questions or "domains" and an additional category to consider "other potential threats to internal validity".[25]

Data analysis

Meta-analysis was performed using mean differences and effect size (Risk ratio) with a 95% confidence interval. To estimate the heterogeneity of the studies, the index I^2 (<25%: weak heterogeneity, 25-75%: moderate heterogeneity, and more than 75%: high heterogeneity) was used. The results were combined using the fixed effect model (Inverse–variance method) in meta-analysis. The Egger test checked the publication bias and Beggs funnel plot, and data analysis was done using STATA/MP. V17 software. A p-value of less than 0.05 was considered significant.

3. Results

After searching with related keywords, 1481 studies were obtained. Endnote.X8 software was used to organize the studies. By using the mentioned software and reviewing the title and abstract of the articles, 394 duplicate studies were eliminated. Then, the abstracts of 889 articles were examined by the researchers. Six hundred forty-three studies that did not meet the inclusion criteria or were excluded due to weak or unrelated relevance to the study objective (if, after reading the title and abstract, it was impossible to decide on the article, the full text was referred to). Two independent researchers carefully reviewed the full text of 246 articles; 58 articles were removed due to low quality, one article was removed due to repetitive content and re-reporting of information in the form of a new article, and 174 studies were excluded due to the inconsistency of study objectives; Finally, 13 articles were selected (Fig. 1).

Characteristics of patients

Seven studies reported breast cancer migration, and six reported breast cancer metastasis (Tables 2 and 3).

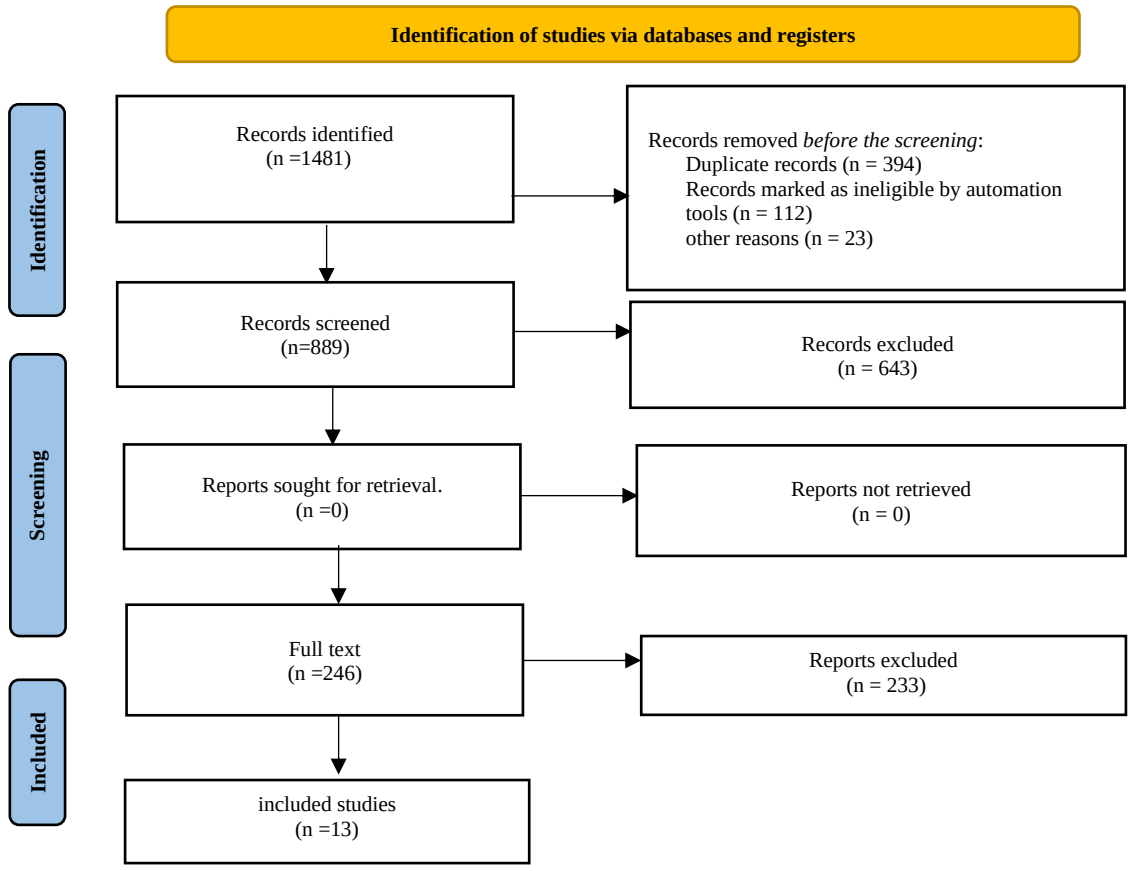

Fig. 1. PRISMA 2020 Checklist.

Table 2. Characteristics of selected studies for breast cancer migration.

Study. Years / Variable	Zhou et al., 2019[26]	Chen et al., 2019[27]	Wu et al., 2019[28]	Alshareeda et al., 2018[29]	Koellensperger et al., 2017[30]	Li et al., 2015[31]	Zhang et al., 2013[32]
Cell Line	MDAMB-231 and MCF-7	MCF-7	MCF-7	MDAMB-231	MDAMB-231 and MCF-7	MDAMB-231 and MCF-7	MCF-7
MSCs Source	hUC	hAD	hAD	hCV	hAD	hUC	hBC

hUC: extracellular vesicles from the human umbilical cord–derived; hAD: human adipose tissue–derived; HCV: human chorionic villi–derived; hBC: human bone marrow–derived.

Table 3. Characteristics of selected studies for breast cancer metastasis.

Study. Years / Variable	Jayaraman et al., 2023[33]	Gonzalez et al., 2017[34]	Meleshina et al., 2015[35]	Lacerda et al., 2015[36]	Ma et al., 2015[37]	Goldstein et al., 2010[38]
Sample Size	RNA-seq dataset	mice	Female athymic nu/nu mice, 4 weeks old, weighing 18 to 20 g	mice	five-week-old female Balb/c athymic nude mice	mice
Cells	MSCs	MSCs	MSCs	MSCs	MSCs	hBMSCs

Effect of human-MSCs on the migration of MDA-MB-231 cells

Mean differences were -0.81 (MD, 95% CI: -0.87, -0.74; I^2 =100% (p=0.00), very high heterogeneity); this result showed human-MSCs from different sources appear to increase the migratory activity of MDA-MB-231 cells compared to the control group (statistically significant level; p<0.01) (Fig. 2).

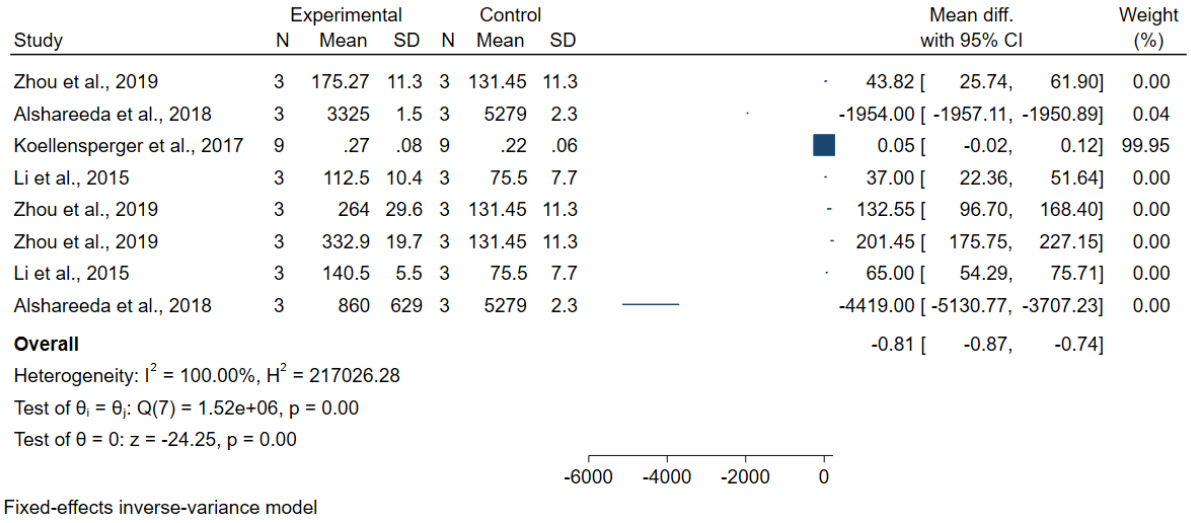

Fig. 2. Forest plots showed an increase in MDAMB-231 migration.

Effect of human-MSCs on the migration of MCF-7 cells

Mean differences were 0.03 (MD, 95% CI: -0.01, 0.08; I^2 =99.45% (p=0.00), very high heterogeneity); this result showed human-MSCs from different sources appear to increase the migratory activity of MCF-7 cells compared to the control group (statistically significant level; p<0.01) (Fig. 3).

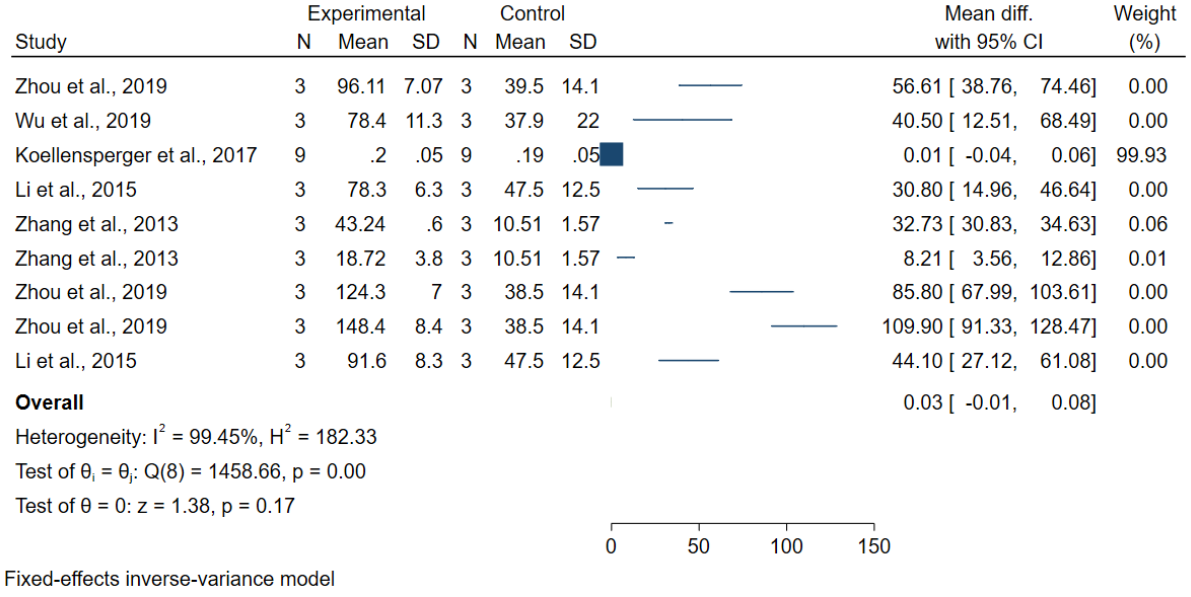

Figure 3. Forest plots showed an increase in MCF-7 migration.

Association between MSCs administration and incidence of metastasis

The risk ratio of incidence of metastasis after MSCs administration was 7.37 (RR, 95% CI: 7.23, 7.53; I^2 =99.86% (p=0.00), with very high heterogeneity); this result showed that administration of MSCs increased the incidence of breast cancer metastasis (statistically significant level; p<0.01) (Fig. 4).

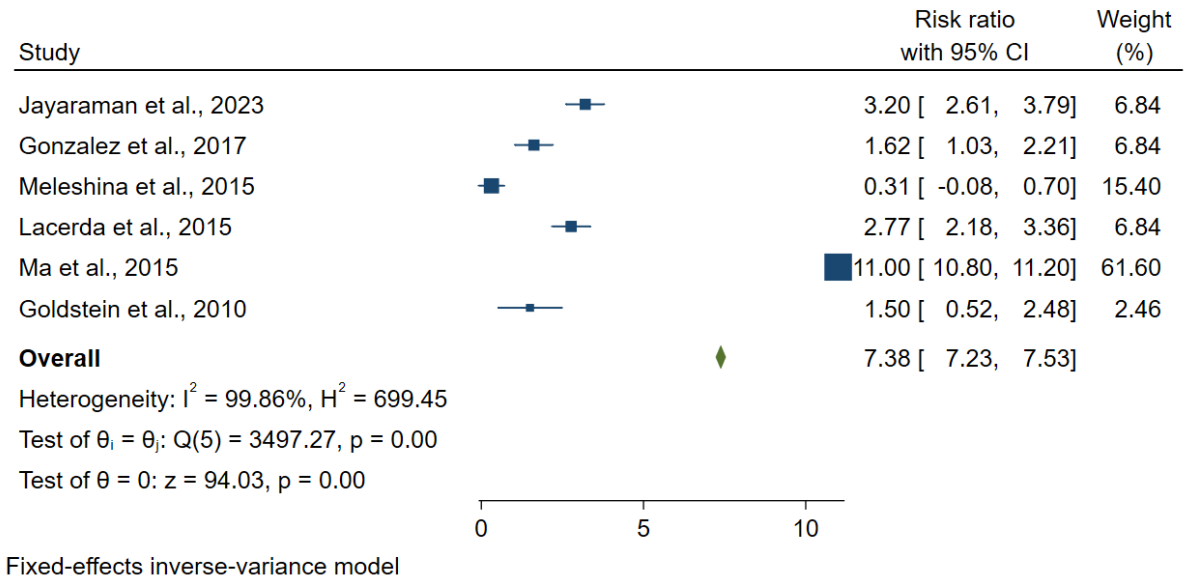

Fig. 4. The forest plot showed the risk ratio of incidence of metastasis after MSCs administration.

4. Discussion

Based on the findings of the present meta-analysis, it was observed that MSCs are effective in cell migration, and this effect was statistically significant. It should be noted that all selected studies have reported the effect of MSCs on cell migration in vitro. The mean difference showed that the migration activity of MDA-MB-231 and MCF-7 cell lines was significantly increased. In the present study, MSCs from different sources were examined, and due to the small number of studies, subgroup meta-analysis was not performed. Studies show that in human adipose tissue, MSCs are more abundant and easily isolated.[39] Evidence also shows that human adipose tissue-derived has more immunosuppressive effects than human bone marrow-derived.[40] In a study, it has been reported that the properties of fetal and human adipose tissue-derived MSCs are better compared to human bone marrow-derived MSCs for immune system modulating function.[41] In the present study, all the selected studies showed that MSCs increase the migration of breast cancer cells. Li et al., 2015) reported a significant increase in the migration of MCF-7 and MDA-MB-231 after extracellular vesicles from the human umbilical cord–derived.[31] There were some limitations in the first part of the present study, such as that most studies examined human MSCs' effect through conditioned media or transwell assays. In the full-text review section of the articles, many studies did not report complete data, so few studies were selected. Studies have shown that there may be a connection between the increase in breast cancer metastasis and MSCs. The present meta-analysis showed that MSCs can increase the number and incidence of metastasis. Of course, the existing studies were mainly in vitro and in vivo. The present study advances the knowledge of pro-metastasis properties of MSCs during breast cancer metastasis. Studies have shown that MSCs are transiently expressed in response to background signals, such as hypoxia at tumor sites, rather than constitutively expressed.[42, 43] It is important to mention that a very high heterogeneity was observed between the studies, which means that the findings of the present meta-analysis should be done with caution. It is necessary to conduct studies with similar cognitive methods to confirm the evidence of the present study.

5. Conclusion

In the present study, only in-vitro and in-vivo studies were examined. Meta-analysis showed that MSCs are significantly effective in increasing the migration of breast cancer cells and metastasis. Therefore, MSCs can be a promising option for treating breast cancer metastases. However, these findings were related to animal models, and pre-clinical studies should be conducted with appropriate cognitive methodology and sample size. Also, more studies that investigate the effects of different sources of MSCs extraction on the progression of breast cancer are needed to complete the findings of the present study.

Conflict of Interest

The authors declared that there is no conflict of interest.

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