INPLASY PROTOCOL

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None declared.

Expression and signaling pathways of Nerve Growth Factor (NGF) and pro-NGF in breast cancer: a systematic review

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Review question / Objective: **This study aims to systematically review and comprehensively summarize the current experimental evidence about the involvement of Nerve Growth Factor (NGF) and pro-NGF signaling pathways in breast cancer. Therefore, the questions are as follows: (1) What is the expression level of NGF, pro-NGF and their receptors in breast cancer? (2) What is the role played by NGF, pro-NGF and their receptors in the pathophysiological mechanisms (i.e., proliferation, apoptosis, angiogenesis, invasion, metastasis) of breast cancer? (3) What is the diagnostic, prognostic and therapeutic potential of NGF, pro-NGF and their receptors in breast cancer?**
Condition being studied: **Breast cancer is a neoplasm of epithelial origin that generally develops in the parts of the breast tissue made up of the glands involved in milk production or in the ducts that connect the glands to the nipple. In women it represents the most frequent cancer as well as the leading cause of cancer death. The incidence of breast cancer is estimated to increase over the years and to reach 3.2 million in 2050, thus representing a health emergency both from a medical and a psychological point of view. Therefore, prevention and early diagnosis of breast cancer appears to be of primary urgency as well as the development of new treatments able to improve its prognosis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 October 2022 and was last updated on 04 October 2022 (registration number INPLASY2022100017).

INTRODUCTION

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NGF, pro-NGF and their receptors in breast cancer? (2) What is the role played by NGF, pro-NGF and their receptors in the pathophysiological mechanisms (i.e., proliferation, apoptosis, angiogenesis, invasion, metastasis) of breast cancer? (3) What is the diagnostic, prognostic and therapeutic potential of NGF, pro-NGF and their receptors in breast cancer?

Rationale: Since the 1990s, several studies have indicated that NGF and its receptors could also play a key role in the pathogenesis of breast cancer and consequently could represent a new therapeutic target. Other evidence indicates that both NGF and its receptors could be considered as accurate diagnostic and prognostic tools for breast cancer. Moreover, the NGF precursor (pro-NGF) signaling pathways were related to breast cancer invasion and metastasis. However, as far as we know, this topic has never been systematically reviewed. Here, we comprehensively summarize and systematically review the current experimental evidence on this topic. The results of this review could be useful to better understand the pathophysiological mechanisms of breast cancer and, consequently, to guide future research.

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METHODS

Search strategy: A systematic search will be carried out in EMBASE, PUBMED and COCHRANE databases. A manual search in the bibliographies of selected articles will be also conducted. Boolean search string will be used, considering free text and Medical Subject Heading [MeSH] terms: ("breast cancer") AND ("nerve growth factor" OR "NGF") OR ("nerve growth factor precursor") OR ("nerve growth factor receptor" OR "NGFR") OR ("tropomyosin receptor kinase A" OR "TrkA") OR ("sortilin") synonyms. All returned results will be systematically identified, screened then extracted for relevant information following the PRISMA guidelines.

Participant or population: Breast cancer patients, cell lines and animal models.

Intervention: Not applicable.

Comparator: Not applicable.

Study designs to be included: There will be no restrictions on the types of study design eligible for inclusion in this review. Any publications that are not in written English will be excluded from the review.

Eligibility criteria: All studies with the aim to understand the role of pro-NGF, NGF and its receptors in breast cancer will be included in the systematic review. Not original research articles (e.g., review, opinion article or conference abstract), articles with unclear design of the study and studies that did not include the role of NGF in breast cancer will be excluded from further analysis. Titles, abstracts, and articles will be evaluated by two separate re-viewers (A.Ma. and F.B.). Titles and abstract will be reviewed for subject relevance. The investigators read full-text versions of eligible articles on their own. Disagreements will be addressed by consensus between the two reviewers. A third investigator (R.M.) will be consulted if the two reviewers reached different decisions or when in doubt. Additional research will be obtained via appropriate publication reference lists and consulting a specialist in the field.

Information sources: The following databases will be used: EMBASE, PUBMED

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and COCHRANE. Also, key journals and reference lists will be searched for additional references. There will be no publication date restriction to avoid excluding papers identified in non-indexed papers. The search date for each database will be reported.

Main outcome(s): (1) Expression level of NGF, pro-NGF and their receptors in breast cancer; (2) role played by NGF, pro-NGF and their receptors in the pathophysiological mechanisms (i.e., proliferation, apoptosis, angiogenesis, invasion, metastasis) of breast cancer; (3) diagnostic, prognostic and therapeutic potential of NGF, pro-NGF and their receptors in breast cancer.

Quality assessment / Risk of bias analysis: We will udes blinding methods among authors using Covidence. Cochrane risk of bias tool will be used. Moreover, disagreements between reviewers will be resolved thanks to a third reviewer/help of expert opinion.

Strategy of data synthesis: The data will be narratively synthesized in subsections according to the outcome (s).

Subgroup analysis: There is no plan for subgroup analysis.

Sensitivity analysis: There is no plan for sensitivity analysis.

Language restriction: Only publications that are written in English will be included in the review.

Country(ies) involved: Italy.

Keywords: breast cancer, nerve growth factor (NGF), TrkA, p75NTR, NGFR, pro-NGF, angiogenesis, invasion, me-tastasis, diagnosis, prognosis, treatment.

Dissemination plans: The review findings will be published in peer-reviewed journals and presented at conferences.

Contributions of each author:

Author 1 - Francesco Bruno - F.B. developed and prepared the review protocol and will also contribute to the selection and data extraction processes. F.B. will also contribute to the preparation the manuscript of this review.
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Author 6 - Raffaele Maletta - R.M. critically reviewed this protocol and is the third reviewer in case of any disagreements. R.M. will also critically review the manuscript of this review.
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