Recent Progress on Telomerase Activity: Focusing on Breast Cancer Treatment in Women

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INTRODUCTION

Cancer is a disease characterized by the uncontrollable division of abnormal cells in the body. It is the second leading cause of death worldwide with the most common cancer-type in the United States being breast cancer[1]. Breast cancer is more common in females than males. In the United States, it is estimated that in 2021, approximately 281,550 women will be diagnosed with an invasive breast cancer[2]. There are some treatment options available to breast cancer patients such as combinational surgical intervention and radiation therapy; however, other avenues such as hormonal, biological, and gene therapy are continuously being explored.

Currently, research of telomeres and the telomerase enzyme has also become a target of interest in anticancer therapeutics because of their roles in cell division. In normal somatic mitotically-dividing cells that have reached cellular senescence, mutations can cause the atypical expression of telomerase. Telomerase causes the DNA of somatic cells to escape senescence, thus potentially leading to uncontrollable cancer cell growth. The enzyme consists of catalytic protein units, one of which is a target of study, human telomerase reverse transcriptase (hTERT). hTERT is the rate-limiting component of telomerase, and the upregulated expression of hTERT represents a surrogate marker of increased telomerase activity in most cancers[3]. If there were a way to inhibit telomerase activity in the somatic cells of the breast, this approach could lead to designs for breast cancer therapeutics. The purpose of this narrative review is to elaborate the effect of telomere-related therapeutics on a population of women with breast cancer.

Method

We conducted our search using the PubMed database for articles relevant to the PICO we developed.

Literature search: The search was conducted using the following database: PubMed. To retrieve information we used the following combination of MeSH terms: [“telomerase” [tw] AND “breast cancer” [mh] AND “women” [mh] AND “treatment” [mh] AND “Therapy” AND “htert” [TW] AND “apoptosis” [tw]. The search period of journal articles was between the years of 2012 - 2022. We retrieved papers in English only.

Inclusion & exclusion criteria: In this narrative review, we screened 17 articles relating to different therapeutic agents that target telomerase as a method of treatment in Breast Cancer cell lines. As we reviewed these articles, we implemented the following inclusion and exclusion criteria: results were narrowed to articles that had been published after 2012 that were cited at least 10 times. When screening articles, we included only those that were of experimental study design.

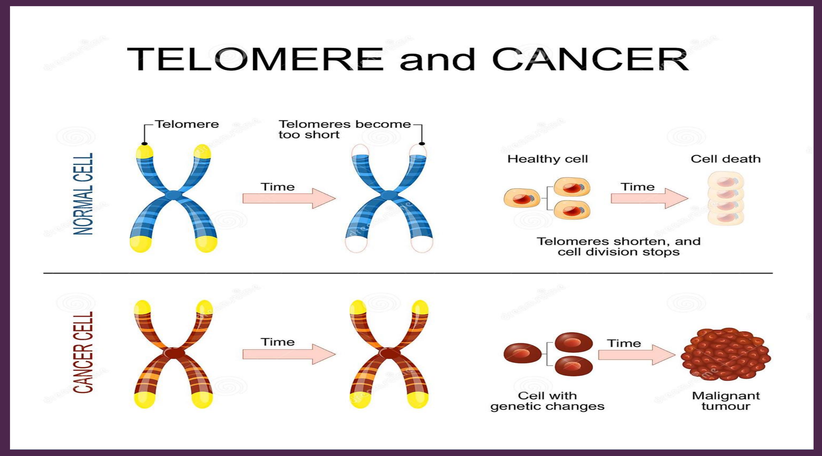
Synthesis of information & management of search results: Each author manually reviewed a selection of articles to determine if all inclusion criteria were met. Results for each study that met our inclusion criteria were input into observation table 1. We compared different therapeutic agents and their impacts on telomerase activity in breast cancer cell lines.

Results

Name of the Study	Year of Publication	Treatment Used	Cell Line Studied	Impact on Telomeres/Telomerase
TGF-beta receptor mediated telomerase inhibition, telomere shortening and breast cancer cell senescence (2016)	2016	BMP-7	MCF-7	BMP7 induces inhibition of telomerase activity and shortening of telomeres in cultured breast cancer cells.
Curcumin and Silibinin Inhibit Telomerase Expression in T47D Human Breast Cancer Cells (	2013	Curcumin	T47D	Curcumin treatment (24h) reduced hTERT mRNA by 80% at 17.5 uM concentration
		Silibinin	T47D	Markedly decreased expression of hTERT with treatment between 5- 17 uM for 24h
		Curcumin-Silibinin Mixture	T47D	Anti-growth and hTERT expression inhibitory effects of the mixture compared to Silibinin and Curcumin alone
Synergistic Growth Inhibitory Effects of Chrysin and Metformin Combination on Breast Cancer Cells through hTERT and Cyclin D1 Suppression	2018	Chrysin and Metformin	T47D	Metformin and chrysin had high synergistic effects in killing cancer cells. In addition PCR demonstrated a significant decrease in cyclin D1 and hTERT gene expression in the T47D breast cancer cell line
Knock-Down of the 37kDa/67kDa Laminin Receptor LRP/LR Impedes Telomerase Activity	2015	Knock-down of LRP/LR by RNAi technology	MDA_MB231, HEK293	Knock-down of LRP/LR by RNAi technology significantly reduced telomerase activity.
A combination of the telomerase inhibitor, BIBR1532, and paclitaxel synergistically inhibit cell proliferation in breast cancer cell lines	2015	BIBR1532, Paclitaxel	MCF-7, MDA-MB-231, BT-474, SK-BR-3	BIBR1532 or paclitaxel alone inhibited proliferation in all cell lines. Combining the two drugs potentiated the effects of telomerase inhibitor
The telomerase inhibitor imetelstat alone, and in combination with trastuzumab, decreases the cancer stem cell population and self-renewal of HER2+ breast cancer cells	2015	Imetelstat (GRN163L), trastuzumab	HCC1569, HCC194, SKBR3, SKBR3-R, TMD-231	Imetelstat inhibits telomerase and cell growth by reducing CSC. There is reduced tumor growth rate when drugs are used in combination; imetelstat amplifies trastuzumab
Influence of mindfulness-based stress reduction (MBSR) on telomerase activity in women with breast cancer (BC)	2014	Mindfulness-based stress reduction (MBSR), control (usual care	N/A study used Peripheral blood mononuclear cells (PBMCs)	MBSR (more favorable psychological status) increases telomerase activity compared to control
Epigenetic-based combinatorial resveratrol and pterostilbene alters DNA damage response by affecting SIRT1 and DNMT enzyme expression, including SIRT1-dependent γ-H2AX and telomerase regulation in triple-negative breast cancer	2015	Resveratrol and pterostilbene	HCC1806, MDA-MB-157, MCF10A	Combinatorial resveratrol and pterostilbene decreased telomerase expression

CONCLUSION

The studies presented in this narrative review elaborate the effect of telomere-related therapeutics on breast cancer prognosis in women through telomerase antagonism alone and the combinatory effects of natural agents as well as chemotherapeutics and telomerase inhibition synergism. Each experimental study yielded statistically significant increased treatment efficacy and thus offers a potential for becoming conventional therapies and even replacing current breast cancer therapeutic regimes.



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