Effect of Physical Exercise in Remodeling Telomere Length and Cancer Prevention in an Epigenetic Prospect – A Systematic Review

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Physical exercise has its impact at the molecular level and aids in healthy well-being of an individual. The current systematic review emphasis on the impact of physical exercise on the telomere length in cancer prevention through epigenetic mechanism. Evidences support the impact of physical exercise in alteration of telomere length through its influence in telomerase activity. The aim of the systematic review is to analyze the effect of physical exercise in remodeling the telomere length in cancer prevention in an epigenetic prospect. Material and Methods: We conducted a qualitative systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The systematic literature search covers articles ranging from the year 2010 to 2020. The Database used for literature searches are PubMed, Cochrane, Science Direct and Google scholar. The Medical Subject Headings (MeSH) used for search include 'Cancer' 'exercise' 'Telomere length' 'telomerase expression'. The outcome variables include the telomere length, telomerase activity, telomere protein stabilizing gene expression status, Micro RNA expression status. Results: After exclusion of irrelevant articles 05 records are selected for final inclusion of the study and are analyzed using a Cochrane risk of bias assessment tool and SANRA tool found to be at low risk of bias and moderate quality respectively. The findings suggest chronic exercise is found to modulate the genetic and epigenetic equilibrium by either up regulation of p53 and p16 expression and stabilizing the telomerase activity within the limits or by increasing the telomerase activity and stabilizing the p53 and p16 expression within limits and impact telomere length, thus maintaining the genetic and epigenetic equilibrium. Conclusion: Based on the evidences collected it can be suggested that chronic moderate intensity aerobic exercise in a lifelong practice shows beneficial effects in a dose-response manner in cancer prevention in a novel way by modulating telomeres through epigenetic mechanism.

Keywords: Breast Cancer; Exercise; Epigenetics; Telomere Length; Telomerase activity.

Physical exercise has its impact at the molecular level and aids in healthy wellbeing of an individual. There are numerous evidences suggesting the effects of physical activity in cancer prevention. The current systematic review emphasis on the impact of physical exercise on

the telomere length in cancer prevention through epigenetic mechanism. Telomeres are the protective cap like structure that is present at the ends of the chromosomes and aids in chromosomal stability. The maintenance of telomeres is essential for the complete DNA replication and for protecting the chromosomes. During each round of cell division the length of the telomeres decreases in length, so on an average the aged cells have a shorter telomere length compared to the young cells, which acts as a biomarker for the identification of the biological age of our cells as opposed to the chronological age. Once the telomeres reaches the terminal length the cell division ceases and the reaches the stage of programmed cell death or apoptosis, the hallmark of cellular aging. Cellular aging (increased cell division) in turn induces cancer development in the presence of instability between p53, p16 expression and telomerase activity.[1,2]

The telomere length is affected by the free radical induced DNA damage. The DNA damage induced by free radical is resolved by DNA repair mechanisms which in turn shortens the telomere length. Evidences suggest females with the highest level of stress found to have shorter telomeres equivalent to one decade on an average when compared to women with low stress level.[1,2] Telomerase is a cellular enzyme which helps in counteracting the shortening telomere length and promotes cellular longevity. The concept of the balanced expression of telomerase and apoptotic gene expression, the longer the telomere length and so the longevity of the cells, is directly or indirectly linked to the prevention of cancer. Shorter telomeres are associated with cancer. Evidences support the impact of physical exercise in alteration of telomere length through its influence in telomerase activity.[1,2]

Evidences also support the influence of epigenetic mechanism in alteration of the telomerase activity. The activity level of telomerase is down regulated by the epigenetic alteration of methylation and histone acetylation. Cellular aging is found to be the major risk factor for cancer initiation. Aging and cancer development share various mechanisms which include genetic instability, shorter telomeres and epigenetic changes. The sedentary lifestyle affects the quality of life and initiates the cancer development through increased telomere attrition. An individual with poor lifestyle is reported to have a shorter telomere length, which increases the risk of cancer development. Physical exercise may have a greater impact in regulating the telomere attrition and cancer prevention. A poor lifestyle increases cellular aging and induces chronic inflammation, oxidative stress and decreases the telomerase activity.[3,4] The aim of the systematic review is to analyze the effect of physical exercise in remodeling the telomere length in cancer prevention in an epigenetic prospect.

MATERIALS AND METHODS

Literature search strategy and study eligibility criteria

We conducted a qualitative systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The systematic literature search covers articles ranging from the year 2010 to 2020. We searched the articles for screening process based on the impact of the exercise on telomere length and telomerase expression in cancer. The Database used for literature searches are PubMed, Cochrane, Science Direct and Google scholar. The Medical Subject Headings (MeSH) used for search include 'Cancer' 'exercise' 'Telomere length' 'telomerase expression'. In the article screening process both full text articles and abstracts are included in the review. The type of study include Randomized controlled trials, Cohort studies, Case control studies, Case reports, reviews. The selection criteria include (i) Problem of research question: Cancer (ii) Exercise protocol includes therapeutic exercise, leisure time physical activity, strength training, aerobic conditioning, rehabilitative exercise, stretching, yoga, flexibility exercises (iii) Frequency, duration and intensity of aerobic exercise (iv) The outcome variable should be telomerase/gene expression status, Micro RNA expression status, Telomere length, and Telomerase activity. Data extraction is performed using Participants/ Problem (P), Intervention (I), Comparison (C) and Outcome (O) format based on the selection criteria and Participants includes Adult with cancer for original studies/ secondary literatures that includes cancer population/ health individuals or animal models as study population that matches the research question, Different types of aerobic exercise is used

as intervention, Comparison can be either control group or same group with results presenting the pre-test and post-test values of outcome variables. The outcome variables include the telomere length, telomerase activity, telomere protein stabilizing gene expression status, Micro RNA expression status. We excluded the articles with following elements (i) Cancer patients with advanced stage (ii) patients in palliative care (iii) Cancer patients with cardio respiratory disease. The articles retrieved are distributed to the reviewers for screening for its eligibility through title screening, abstract screening and full text screening. The feedback and comments from reviewers are discussed and resolved.

Data extraction

The citations collected after eligibility screening processes for data extraction. The relevant data extracted from the studies included are updated in the data extraction sheet. Disagreements are resolved after discussions with the reviewer's opinion. The elements included for data extraction are: (i) Author and year of study (ii) study design (iii) Population/ Problem (iv) Comparison status like control group/comparison within same group (v) intervention – type of exercise (vi) Intensity, duration and frequency of exercise (vii) Telomere length/Telomerase activity / Gene expression/ Micro RNA expression status (viii) Results and conclusion of study.

Risk of bias assessment

The risk of bias of the articles included in the systematic review are assessed using the Risk-of-bias visualization (robvis) assessment tool – ROB2 tool for Randomized controlled trials respectively. The risk assessment domains include i) Bias due to randomization ii) bias due to deviations from intended interventions iii) bias due to missing data iv) bias due to outcome measurement v) bias in selection of reported result and the overall risk of bias. The judgment for each article is given as low risk, some concerns, high risk.[5,6] The quality of the extracted narrative traditional type review articles are assessed for its quality using Scale for the Assessment of Narrative Review Articles - SANRA tool.[7] The domains include i) Justification of article's importance for readership ii) Statement of concrete aims or formulation of questions. iii) Description of the literature search iv) Referencing v) Scientific

reasoning vi) Appropriate presentation of data. The domains are graded between 0 and 2 to imply as low and high quality.

RESULTS

Literature search results

We extracted the data using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We retrieved unique citations from different sources of databases including 14 records from PubMed database, 16 records from Cochrane database, 410 records from the Science Direct database and 16,600 records from Google scholar database. In total 17,040 records were extracted. During the screening process 470 records are selected for title screening process that matches study eligibility criteria, the other articles are eliminated from the study as they did not fit into the inclusion criteria. In the process of title screening, 44 records are selected for the abstract screening process after eliminating records where exercise is not used as an intervention to analyze the telomere length or telomerase activity. After exclusion of irrelevant articles 05 records are selected for final inclusion of the study that satisfies the elements of research question. The reason for elimination of records into study includes the i) study design ii) telomere length or telomerase activity is not used as outcome measure iii) duplication of articles iv) study population not matched with inclusion criteria. (Figure 1)

Characteristics of included studies

The articles included in the review process range from 2010 to 2020. After the screening process five articles are selected for the inclusion in the study that satisfies the study eligibility criteria. Among five, two studies are randomized controlled trials and three articles are literature reviews which are secondary sources. The final records included for the systematic review shows heterogeneity in its study design and study population. Though heterogeneity exists between the selected articles (two randomized controlled trials and three literature reviews), due to lack of enough evidence relevant to the research question, three records with literature review is also selected as it satisfies the study eligibility criteria. The study population included are, Breast cancer survivors, includes both human and animal

models, and healthy individuals. Aerobic exercise is the interest of interventions delivered in different modes like supervised, home –based exercise, recreational physical activity, all of which includes activities like walking, cycling, jogging ranging from moderate to vigorous intensity of exercise. Nezamdoost et al 2020 in a randomized controlled trial analyzed the effect of four week high intensity interval training (HIIT) in female breast cancer mice and determined the effect of exercise in Sirtuin -1 SIRT-1 (Silent information regulation factor -1- histone acetylation enzyme), h TERT (human telomerase reverse transcriptase) expression and tumor suppressor gene p53 expression status in comparison with the control group.[8] Tara Sanft et al, 2018 in a randomized controlled trial analyzed the effect of physical exercise in breast cancer survivors. The intervention protocol includes 150 minutes of moderate intensity aerobic exercise / week and 10,000 steps per day which is calculated using pedometer for duration of six months period. The changes in the leucocyte telomere length is determined in the intervention group in comparison with the control group (with usual care). The relative telomere length (RTL) is measured at baseline and at six months using quantitative PCR.[9] Nikitas N Nomokos et al 2018 in their literature review collected evidence to justify the role and the linkage of exercise and shorter telomere length and the telomerase activity. The evidence attempts to prove the reduction in the telomere attrition followed by the exercise intervention which in turn reduces the cancer risk. The attenuation of telomere attrition is achieved by reducing the oxidative stress and chronic inflammation followed by the exercise intervention. [4] Kalliopi Adraskela 2017 in their literature review collected evidences with regard to intensity, duration and frequency of aerobic exercise intervention in breast cancer survivors and measured the outcome variable with potential pathophysiologic pathways which includes oxidative stress, global DNA methylation status and changes in the telomere length, telomere stabilizing proteins, methylation status of p53 gene through gene activation or gene silencing .[10] Massod A Shammas ,2011 in her literature review collected evidence to highlight the importance of telomeres in wellbeing of human and cancer and summarized the effect of exercise in preventing cancer by altering the length of telomeres, telomerase activity and with p53 and p16 gene expression.[11] (Table - 1)

Results of Risk of Bias Assessment

The Randomized controlled trials that are selected for inclusion are assessed by ROBINS Cochrane Risk of bias assessment tool and are found to be at low risk of bias. The selected narrative reviews are assessed for its quality using Scale for the Assessment of Narrative Review Articles - SANRA tool and found to be at moderate quality.[6,7]

Results of Impact of exercise in p53 and p16 m RNA expression and telomerase activity in cancer

Nezamdoost, 2020 in an animal model reported the anticancer effect of high intensity interval training (HIIT). The findings reported the exercise training acts as a protective factor in altering breast cancer. The m RNA expression of p53 was increased in intervention group with significant difference in comparison to the control group. At the same time no significant difference is observed in the hTERT mRNA expression between groups. The up regulation of p53 expression in the tumor tissue prevents carcinogenesis by tumor suppression pathway[8]. Nikitas N Nomokos, 2018, reported the increasing the level of physical activity to be associated with elevation of telomerase activity and suppression of m RNA expression of p53 and p16 apoptotic gene activity. Decreased level of expression of these protein is linked to protection of telomeres. These findings suggest that in a more balanced conditioned environment, the need to larger expression of protective sheltering proteins is not necessary. This conditioned balanced environment may be created by the chronic moderate intensity aerobic exercise.[4]

Results of Impact of exercise and relative leucocyte telomere lengthening in cancer

Tara Sanft, 2018 conducted a randomized controlled trial in breast cancer survivors and reported the change in relative length of leucocyte telomere. The findings suggest difference between the intervention and comparison group. Relative to the baseline data, the participants in the intervention group found to have 3% lengthening in the relative telomere length compared to 5% reduction in the relative length in the usual care group (0.02 ± 0.22 vs -0.44 ± 0.20) with a difference of 0.06, and p = 0.12. Over the six month intervention period

Table 1. Characteristics of Included studies

Author and Year	Study Population/ Problem	Type of Study	Comparison group	Intervention	Intensity / duration/ frequency of exercise	Telomere length/ Telomerase activity/ gene expression status	Conclusion
Nezamdoost et al , 2020 (8)	Breast cancer in female BALB/c mice	RCT	Control group	Aerobic exercise	Four week High intensity interval training (HIIT)	SIRT -1 (silent information regulation factor 1- histone acetylation eezyme), hTERT (telomerase reverse transcriptase) expression and p53 gene expression was determined by real time PCR. The m RNA p53 expression and m RNA level of SIRT 1 was increased in intervention group compared to other group. No significant change was found in hTERT expression between groups in four weeks.	The findings conclude the HIIT may reduce the tumor risk thorugh upregulation of p53 gene which is associated with tumor suppression and HIIT did not alter the hTERT expression status . significantly in four weeks
Tara Sanft et al 2018 (9)	Breast cancer survivors	RCT	Breast cancer survivors	Aerobic Exercise with usual care	150 Minutes per week of moderate intensity aerobic activity and 10,000 Steps / day calculated using pedometer for six months period	The changes in leucocyte telomere length – Relative Telomere Length (RTL) increased by 3% in the intervention group and decreased by 5 % in the usual care group. Stage 0/I cancer population - 7% lengthening when compared to 8% shortening in usual care group. No significant difference was observed in stage II/III cancer population	The findings of the study concluded that the exercise practice in stage 0 and stage I breast cancer survivors may impact to lengthening of telomere compared to shortening of the telomere in the usual care group.
Nikitas N Nomikos, 2018 (4)	Cancer population/ Healthy individuals/ animal models	Literature Review	-	Aerobic Exercise intervention	Chronic moderate intensity exercise/ recreational physical activity/ vigorous exercise	Exercise have greater effect in attenuating telomere attrition. Increased level of physical activity is associated with increased telomerase activity and reduction of apoptosis proteins (p53 and p16).Vigorous exercise above threshold limits could reduce the p53 activity and decrease expression of proteins related to protection of telomere	Regular moderate intensity physical exercise leads to decrease telomere attrition and diminish the risk of cancer through reducing oxidative stress and chronic inflammation and thus reducing cancer risk

Author	Population	Study type		Intervention	Key findings	Conclusion
Kalliopi Adraskela et al, 2017 (10)	Breast cancer survivors	Literature review	-	Aerobic Exercise intervention	Chronic exercise of moderate intensity/ strength training, flexibility exercise, resistance exercise	The chronic moderate intensity exercise enhances inflammation related gene expression. Exercise positively impacts telomeres by promoting the expression status of telomere stabilizing proteins and reduces oxidative stress by global DNA hypomethylation, regional hypermethylation of tumor suppressor gene through gene silencing and protooncogene activation which inturn telomere length	The evidences conclude chronic moderate intensity aerobic exercise impacts the telomere length and telomerase activity by influencing it gene expression status and telomere length acts as protective mechanism and biomarker for Breast cancer
Masood A. Shammas, 2011 (11)	Cancer population/ Healthy individuals/ animal models	Literature review	-	Aerobic Exercise intervention	Chronic exercise of moderate intensity/ strength training, flexibility exercise, resistance exercise	The frequency and intensity of exercise is inversely correlated with the biomarkers for the DNA damage, Telomere length, and telomerase activity and with p16 expression. Exercise reduces oxidative stress and protects Telomeres. Exercise is has its positive impact in elevating telomerase activity and reducing p53 and p16 expression. Exercise is associated with increased telomerase activity, reduced telomere attrition, and elevated telomere stabilizing protein expression by reducing oxidative stress.	Evidences concludes regular moderate intensity exercise aids to shorten the leucocyte telomere length and increases the telomerase activity. It reduces the oxidative stress there by activating the expression of telomeres stabilizing proteins and thus aids in cancer prevention.

stage 0/I patients in the study group found to have 7% relative telomere lengthening as compared to 8% shortening in stage 0/I patients in usual care group with a p value - 0.0004. On the other hand there was no significant difference between groups for stage II/III with p=0.30. The effect of telomere lengthening was found to be stronger in patients with stage 0 and stage I in the intervention group.[9]

Results of Impact of exercise in Telomere lengthening, Telomerase dynamics and cancer

Nikitas N Nomokos, 2018 in their literature review, reported telomeres as a specialized DNA complexes that prevention terminal attrition of eukaryotic chromosomes. Telomerase on the otherhand is an enzyme required for the synthesis of telomeric DNA for its relative lengthening. A specialized protein subgroup of telomerase is a telomerase reverse transcriptase (TERT). An effective modulation of telomerase activity, TERT expression is said to have an anti-cancer property. Telomeres shorten with each round of mitosis due to oxidative stress that induces DNA damage, and inability of the DNA replication mechanism called

as end replication problem. Evidences support that shorter telomeres are associated with cancer due to inadequate physical activity that leads to chronic inflammation, increased oxidative stress and decrease in telomerase activity. Evidence reported the exercise to have a great effect on attenuating telomere attrition. Studies conducted using animal models reported the effect of exercise to have in attenuating cell senescence and protects telomere length.[4]

Kalliopi Adraskela 2017, reported the extent of exercise induced reduction in breast cancer risk varies based on the type and duration of exercise. There are different type of physical activity like recreational activity which is performed at leisure time for enjoyment, occupation related physical activity, house hold activities, transportation related activities, aerobic exercise or endurance training like brisk walking jogging, jogging, strength resistance training like weight lifting and balance training and flexibility exercises. Each type of activities is said to have its own effect in cancer prevention. Studies
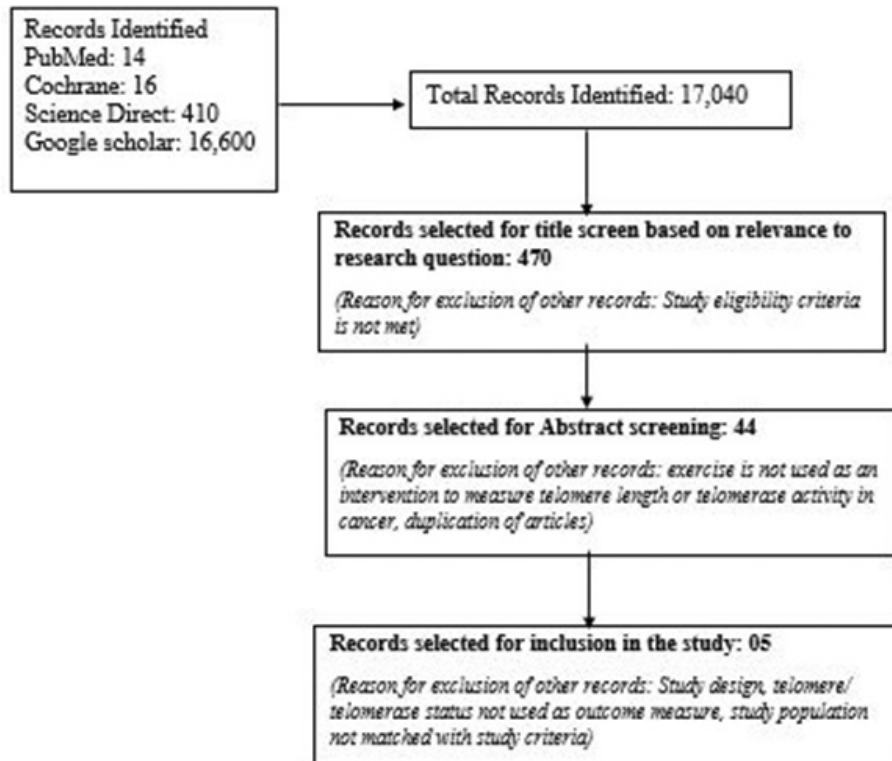

Fig. 1. Data screening process

reported that 21% of risk reductions are linked with recreational and household activities, 18% are found to be linked with occupational activities, and 13% is linked with walking and cycling type of activities. Evidences support dose –response relationship between exercise and breast cancer risk. More researches supports exercises with greater higher frequency and longer duration to have a greater beneficial effect in breast cancer prevention. Two to three hours of exercise per week is associated with 7% risk reduction. Six hours per week of exercise per week is associated with 30% of risk reduction. Based on the intensity of the exercise it is classified as light, moderate and vigorous. 26% risk reduction is associated with vigorous physical activity and 22% risk reduction is associated with moderate intensity physical activity. To encapsulate long term practice of moderate to vigorous recreational physical activity over life time is suggested to have beneficial effect in breast cancer risk reduction. Evidences support the different types of exercise not only has its impact in prevention stage but also has its role in stages after diagnosis and treatment.[10]

Massod A Shammas, 2011 in his literature review suggests the duration, intensity of exercise inversely correlated with the biomarkers of DNA damage like changes in telomere length, m RNA expression of p16. The exercise modulates the metabolic activity of lipids and leads to reduction in the oxidative stress and protects DNA and telomeres through telomerase activity. Evidences reported that exercise increases the telomerase activity followed by the suppression of the expression of apoptotic genes including p53 and p16 in mice. The studies conducted in human trials also reported to have elevated telomerase activity which reduces the relative shortening of telomere length. It maintains the telomere length by elevated telomerase stabilizing proteins and protects the cell from apoptosis.[11]

DISCUSSION

To summarize the findings of the study, Lifelong practice of moderate intensity aerobic exercise is found have a dose response based beneficial effect in cancer prevention thought it epigenetics modulation. The interplay of exercise, expression of telomerase, the telomere stabilizing proteins and the m RNA expression of apoptotic gene / tumor suppressor genes p53 and p16 plays a major role in changing the relative telomere length. The exercise is found to modulate the genetic and epigenetic equilibrium by either up regulation of p53 and p16 expression and stabilizing the telomerase activity within limits or by increasing the telomerase activity and stabilizing the p53 and p16 expression within limits and thus maintaining the genetic and epigenetic equilibrium.

Kalliopi Adraskela 2017, based on evidences in their literature review reported that the basic pathogenesis of breast cancer to be the production of free radicles that leads to oxidative stress. These unpaired electrons are unstable and cause damaging effects on the lipids, carbohydrates, proteins and nucleic acids. These effects has its impact in the epigenetic regulation and modulation of gene expression. The unstable reactive nature of free radicles is said to cause global DNA hypomethylation and affects the epigenetic modulation of tumor suppressor genes, apoptotic genes leading to alteration and the inturn affects the telomerase activity. The alteration in the telomerase expression can affect the telomere length in cancer. It activates the oncogenes and suppress the activity of tumor suppressor gene. The oxidative stress inturn reduces the telomere length by defective telomerase activity. Reports suggest telomerase dysfunction and telomerase reactivation is linked with high risk for cancer as it protects the defective cell from apoptosis and allows the cells proliferation. This is highly influenced by the activity of defective modulation of tumor suppressor gene and apoptotic gene expression. The type of exercise, its duration and frequency has its impact in preventing breast cancer risk through prevention strategies. The chronic moderate intensity exercise is said to act as a preventive measure by reducing the oxidative damage, acts as a modulator for epigenetic regulation of oncogene, tumor suppressor gene, apoptotic gene, and telomerase expression. At the same time vigorous exercise above threshold limits when tested is found to cause raise in the free radical production.[10,12–15]

Oakley - Girvan I in 2017, in their population based sample, analyzed the impact of exercise in leucocyte telomere length in premenopausal breast cancer survivors. This is a

randomized controlled trial of 273 premenopausal women, 55 years of age. The relative telomere length is assessed before and after the exercise intervention. The participants with longer telomeres at the time of study are found to have shorter growth of leucocyte telomere length in the post intervention analysis when compared with those participant who had shorter leucocyte telomere length before exercise intervention, which is in agreement with current study. [16,17]

Dean Ornish, 2008 analyzed the impact of exercise on increased telomerase activity in 30 men diagnosed with low risk prostate cancer. The study reported that peripheral blood mononuclear cells (PMBC) telomerase activity is found to increase the expression of telomerase from 2.00 to 2.22 with p value 0.03. The raise in the telomerase expression is significantly associated with decrease in low density lipoprotein and cholesterol and modulating the telomerase maintenance capacity in human immune system cells which is in agreement with our study.[18–20]

Christine M Friedenreich, 2018, conducted a randomized controlled trial of aerobic activity in comparison with inactivity. The study participant includes 212 physically inactive disease free post-menopausal women. The exercise intervention includes forty five minutes of aerobic exercise per day for five days per week achieving maximum 70% - 80% heart rate reserve. The base line measurement of telomere length and post intervention after 12 month period was analyzed using q PCR. The highlight of the study includes exercise reduces the cancer risk but the pathophysiologic mechanisms behind are imprecise. The average change in the telomere length was 13% for intervention group and 8% for the control group which is in agreement with current study, however the change in the telomere length was not significantly different between two groups.[21–23]

Warrick L Chilton, 2014, analyzed the acute exercise induced response of telomere genes and micro RNA in 22 healthy male participants. The intervention includes thirty minutes of treadmill running at 80% peak oxygen uptake. The base line analysis was done followed by post intervention analysis sixty minutes post exercise. The telomerase reverse transcriptase (TERT) m RNA expression was found to be significantly different with p = 0.001, SIRT6- Sirtuin m RNA expression was upregulated with p <0.05. The results suggest aerobic exercise to be sufficient to influence the key telomeric genes and miRNA in white blood cells, which is in agreement with current study.[24–27] Nicole C Arsenis, 2017, in their review reported more observational studies to have higher levels of physical activity linked with increased telomere length. The evidences support that telomere length has inverse association with cancer. Exercise is found to have beneficial effect in maintenance of telomere length. The study also recommends future researches to confirm the findings, the dose and intensity of exercise protocol to have its beneficial effect on telomere length which is in agreement with the study.[28–30]

Limitations of the systematic review

Number of limitations are involved in the systematic review in giving the exact intensity, frequency and duration of aerobic exercise and its impact in the telomere length and telomerase expression. We are able to find associations between aerobic exercise and relative telomere length, m RNA expression of telomerase stabilizing proteins, apoptotic and tumor suppressor gene expression p53 and p16. Though the results prove beneficial association, its evidences are inconclusive in cancer patients, which addresses the importance of future studies in large scale.

Strengths of the review

Based on the evidences collected, the number of studies that associates Physical activity, telomere length in cancer in an epigenetic prospective is very limited. The knowledge, awareness and practice towards cancer prevention in epigenetic point of view is highly recommended. Evidences collected through this systematic review helps to unfold the existing lacuna in this field of research and also explores the hidden science behind the approach for cancer therapy and prevention. The review study also insists the need for the practicing health professionals to view the cancer prevention strategies in an epigenetic perspective.

Recommendation for future research

The current systematic review explores the current lacuna existing in the research field with respect to the approach of cancer prevention and treatment strategies in an epigenetic context. We recommend to perform number of future studies

with large sample size to analyze the interplay between the exercise, telomere length, telomerase activity and p53, p16 expression in cancer risk. It can help us to understand the science behind the process of tumerogenesis to approach the cancer preventive strategies in an epigenetic context.

CONCLUSION

Based on the evidences collected within the limitations of the current systematic review, it can be suggested that chronic moderate intensity aerobic exercise in a lifelong practice shows beneficial effects in a dose-response manner in cancer prevention. The findings suggest that chronic practice of exercise is found to modulate the equilibrium of protein expression by either up regulation of apoptotic and tumor suppression gene expression and limiting the telomerase activity or increasing the telomerase activity and limiting the apoptotic gene expression thus maintaining the genetic and epigenetic equilibrium. Even though we lack enough evidence, we believe the review will open up opportunities to dig into the hidden science behind the process of tumerogenesis in cancer prevention and prognosis. To encapsulate, the systematic review explores the epigenetic science behind the process of carcinogenesis that can aid us to plan our preventive and therapeutic pathway for cancer risk in a novel way.

ACKNOWLEDGEMENT

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