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# Mitochondrial DNA Mutations and Oxidative Phosphorylation Reprogramming in Colorectal Cancer and Breast Cancer: Systematic Review of Distinct Mitochondrial Mechanisms in Tumor Progressions

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**ABSTRACT**

**Background:** Mitochondrial dysfunction with mitochondrial DNA (mtDNA) mutations and oxidative phosphorylation (OXPHOS) reprogramming have a significant role in cancer progression. The aim of the study was to mechanically compare different mechanisms of mitochondria in tumour development, both in breast and colorectal cancer. **Methodology:** It was a systematic review based on PRISMA guidelines 2020. The databases used in the search were PubMed, Scopus, Web of Science, and Google Scholar from 2020-2026. This was done by including clinical, experimental in vitro and in vivo studies that examined the role of mitochondrial DNA mutations and OXPHOS pathways in breast and colorectal cancer and excluding reviews, case reports, non-English studies, and irrelevant disease models. Newcastle-Ottawa Scale (NOS), Joanna Briggs Institute (JBI) checklist, ROBINS-I tool, modified in vitro tools, and SYRCLE tool were all used to assess risk of bias, with some certainty of evidence assessed using the GRADE framework. **Results:** 12 studies meet the inclusion criteria. Results have shown that OXPHOS reprogramming and the presence of the mutations in the mitochondrial DNA resulted in electron transport dysfunction, reactive oxygen species generation, and ATP production, all of which were contributing factors to tumour progression, metabolic adaptation, and therapeutic resistance. Mitochondrial pathways also had an effect on tumor microenvironment and prognosis. The risk of bias was moderate in general and the certainty of evidence was low according to GRADE assessment. **Conclusion:** Mitochondrial changes are the main focus of cancer development and are potential therapeutic targets. It is recommended that future research should be done on clinical validation and development of mitochondrial-targeted therapy to treat cancer on a personal basis.

**Keywords:** Mitochondrial Dysfunction, Oxidative Phosphorylation, Mitochondrial DNA, Reactive Oxygen Species, Breast Cancer, Colorectal Cancer, Neoplasms

## Introduction

Mitochondrial dysfunction had been progressively identified as a hallmark of cancer, which plays an important role in tumour emergence, growth and therapy resistance [1]. The Warburg effect had been traditionally used to describe cancer metabolism, but emerging data had shown the importance of mitochondrial oxidative phosphorylation (OXPHOS) in the bioenergetics of tumours and tumour survival [2,3]. Mitochondria participated in not only energy production, but also in apoptosis regulation, redox regulation, and cellular signalling pathways that had a role in tumour progression [4]. Metabolic plasticity in colorectal cancer (CRC) and breast

cancer (BC) had already allowed tumour cells to alternate between glycolysis and OXPHOS on changing environmental conditions, increasing the tumour aggressiveness and adaptability [5,6]. As a result, mitochondrial reprogramming had become a fundamental part of cancer biology and one of the possible treatment targets.

Among these mitochondrial changes, mitochondrial DNA (mtDNA) mutations and mitochondrial reprogramming of OXPHOS were recognised as critical parameters that affect tumour behaviour and that the mutations of mitochondrial DNA (mtDNA) encoded important components of the electron transport chain (ETC), and these mutations had been reported to disrupt mitochondrial activity, enhance reactive oxygen species (ROS) production, and stimulate oncogenic signalling pathways [7,8]. The functional relevance of the mitochondrial DNA mutations in tumour metabolism and immune response could also be actively remodelled and found a role in cancer development. OXPHOS dysregulation was also linked with increased energy metabolism, epithelial -mesenchymal transition (EMT), and chemotherapy resistance. The gene signatures of OXPHOS-mediated mitochondrial changes and mitochondrial modifications had been fractionated into tumour progression and prognosis in CRC and metastasis and therapeutic resistance in BC. This highlighted the interplay between the role of the mutations of the mitochondrial DNA and metabolic reprogramming in tumour development [9,10].

Despite of evidences, a number of gaps remained in the interpretation of the specific and overlapping functions of both the role of mutations in the mitochondrial DNA as well as OXPHOS reprogramming in various cancers. These mechanisms were mostly studied separately or in specific types of cancer and had not been compared to make comparative conclusions before. Moreover, inconsistency in study design, sample size and experimental model had created disparities in reported results. There has been an insufficiency of thorough synthesis of both genetic and metabolic alterations in the mitochondria in terms of links between CRC and BC. Thus, systematic review of existing literature was required to elucidate these processes and find possible translational uses.

This systematic review was done to assess the importance of mitochondrial DNA mutations and oxidative phosphorylation reprogramming in colorectal and breast cancers. It aimed to integrate available evidence to establish the role of these mitochondrial mechanisms in tumour progression, metabolic adjustment and therapy response as well as finding possible biomarkers and therapeutic targets.

## Methodology

The systematic review was conducted following PRISMA 2020 guidelines [11].

**Inclusion and Exclusion Criteria:** Original research articles, such as experimental (in vitro/in vivo), observational and clinical studies, investigating the mechanistic role or therapeutic potential of the involvement of mtDNA mutations and/or OXPHOS reprogramming in CRC or BC, were included. Only English studies were taken into consideration. The articles were excluded if they were review articles or editorials or conference abstracts or non-primary research or when they did not directly evaluate mitochondrial mechanisms in tumour progression or therapy. Articles that lacked full texts were also not included as shown in Figure 1.

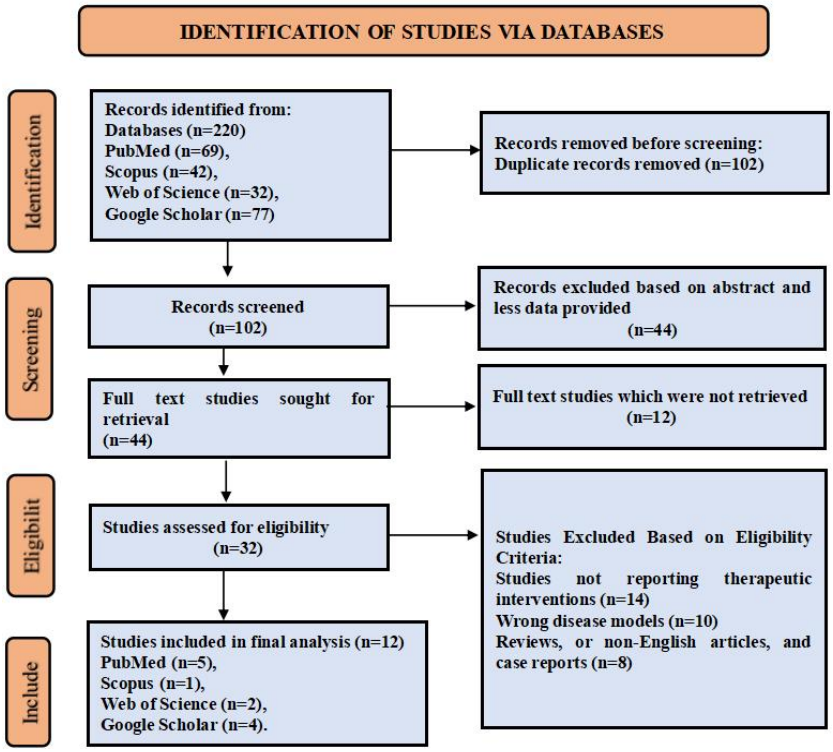


*Figure 1: PRISMA Flow Diagram for Study Selection. The flowchart was designed according to the PRISMA guidelines 2020, showing study identification, screening, assessment eligibility, and final selection in the systematic review.*

**Data Sources and Search String used:** Search was done from electronic databases such as PubMed, Scopus, Google Scholar, Web of Science, and Cochrane Library to retrieve relevant literature published between January 2020 to January 2026 The search used both a combination of MeSH terms and free-text words relating to mitochondrial dysfunction and cancer metabolism The search terms were, “Mitochondrial DNA mutations”, “mtDNA”, “Oxidative phosphorylation”, “OXPHOS”, “Mitochondrial reprogramming”, “Colorectal cancer”, “Breast cancer”, “Tumour progression” and “Metabolic reprogramming”. Boolean operators (AND, OR) were used and the reference list of the selected articles was screened manually to get other relevant studies. The representative search strings were: ((“mitochondrial DNA mutations” OR “mtDNA alterations” OR “mitochondrial genome instability” OR “mtDNA copy number”) AND (“oxidative phosphorylation” OR “OXPHOS” OR “mitochondrial metabolism”

OR “bioenergetic reprogramming”) AND (“colorectal cancer” OR “colon cancer” OR “breast cancer” OR “triple-negative breast cancer”) AND (“tumour progression” OR “metastasis” OR “cancer progression”)).

**Study Selection and Data Extraction:** The two reviewers independently extracted data. The information that was extracted was the author and year, the study design, type of cancer, sample size, molecular pathways (mtDNA mutations and OXPHOS), main findings, and therapeutic implications. Any differences during data extraction were clarified either by discussing or referring to a third reviewer. Data extraction was done in the standardised form: author, year, cancer type, study design, mitochondrial target/pathway, Therapeutic interventions, and outcomes.

**Primary Outcome and Quality Assessment:** The risk of bias was assessed using design-specific tools, including the Newcastle-Ottawa Scale (NOS), JBI checklist, adapted ROBINS-I, SYRCLE tool, and a modified in vitro assessment framework [12,13]. Each study was categorised as having low, moderate, or high risk of bias. The overall certainty of evidence was evaluated using the GRADE approach.

## Results

Database search found 220 records, 69 in PubMed, 42 in Scopus, 32 in Web of Science, and 77 in Google Scholar. A total of 118 records were left after the elimination of 102 duplicate articles; 102 records were filtered by the titles and abstracts. After the screening, 44 studies were eliminated because of inadequate data or irrelevance. Lastly, 12 studies were identified to meet all inclusion criteria and hence were included in the systematic review. Among them, 5 articles were found in PubMed, 1 in Scopus, 2 in Web of Science, and 4 in Google Scholar. Table 1 summarizes the characteristics of included studies investigating mitochondrial DNA (mtDNA) mutations and oxidative phosphorylation (OXPHOS) reprogramming in breast cancer and colorectal cancer. The table includes study design, sample size, molecular mechanisms, key findings, and therapeutic implications.

**Table 1: Summarized view of characteristics of 12 studies selected**

| Author and Year | Study design (Cancer type) | Sample Size (Study Characersitics / Scheme of Groups) | Molecular Mechanisms (Pathway) | Outcomes / Key findings | Therapeutic implications / Interventions |
|---|---|---|---|---|---|
| **Hu et al., 2020** [14] | Clinical and experimental in vitro study (Breast cancer) | n=404 women (breast cancer)<br><br>Cell lines: (MDA-MB-468, MCF-7, MDA-MB-231) | OXPHOS pathway<br><br>Osteogenic differentiation (RUNX2, BMP2, OPN, ALP), EMT (E-cadherin/N-cadherin), mitochondrial metabolism (OCR/ECAR, ROS) | Calcifications promote osteogenic differentiation, proliferation, migration, invasion, and metabolic activity | Target osteogenic differentiation, EMT, and mitochondrial metabolism to reduce bone metastasis risk |
| **Evans et al., 2021** [15] | Clinical and in vitro study (Breast cancer) | n=43 patients (Breast cancer)<br><br>Cells: (BCX.010 PDXs; MDA-MB-468 cells) | OXPHOS pathway<br><br>OXPHOS metabolism (IACS-10759 target), AXL signaling, cell cycle (Palbociclib), DNA repair, HDAC signaling | OXPHOS inhibition reduced tumor growth, synthetic lethal partners identified, combination therapies enhanced efficacy | Target OXPHOS alone or with AXL, CDK4/6, PARP, or HDAC inhibitors for TNBC therapy |
| **El-botty et al., 2023** [16] | Clinical cohort study (Breast cancer) | n=503 patients (Breast Cancer) | OXPHOS pathway<br><br>Mitochondrial OXPHOS, cell cycle, ER signaling, metabolic stress, MRPS12/NDUFS6-related mitochondrial translation | OXPHOS inhibition reduced PDX tumor growth; MRPS12/NDUFS6 expression correlated with metastasis-free survival | Target mitochondrial respiration with IACS-010759, combine with Palbociclib or endocrine therapy |
| **Vikramdeo et al., 2023** [17] | Clinical cohort study (Breast cancer) | n=32 (TNBC patients),<br><br>n=9 patients (cancer-free controls) | mtDNA mutations<br><br>Mitochondrial DNA (mtDNA) mutations, mitochondrial electron transport chain | TNBC tumors showed enriched mtDNA mutations, altered mtDNA content, and reduced NDUFB8/SDHB expression | Target mitochondrial metabolism and oxidative phosphorylation |
| **Cruz et al., 2020** [18] | Clinical observational study (Breast cancer) | n=82 patients<br><br>(frozen tumor and matched normal tissue) | mtDNA mutations<br><br>Mitochondrial DNA (mtDNA) copy number, D-loop region sequencing, mtDNA haplogroups (A2, B2, B4, C1, D1), mitochondrial-nuclear | mtDNA content varied by histological subtype, age, menopause, and haplogroup; some haplogroups (e.g., C1) showed significantly lower mtDNA copy number in tumors vs | mtDNA copy number and haplogroups may serve as biomarkers for tumor biology and risk stratification |

| | | | | | |
|---|---|---|---|---|---|
| | | | DNA ratio | normal tissue | |
| **Si et al., 2020** [19] | In vitro study (Breast cancer) | Human breast cancer cell lines<br><br>(Breast cancer, MDA-MB-231 and MCF-7 cells) | mtDNA mutations<br><br>Mitochondrial dynamics (MFN1, MFN2, OPA1, DRP1), ROS generation, oxidative stress, mitochondrial biogenesis | Silibinin treatment inhibited cell proliferation, migration, invasion; reduced ROS and ox-mtDNA; promoted apoptosis | Silibinin may serve as a therapeutic agent targeting mitochondrial dysfunction. |
| **Martinez-Bernabe et al., 2024** [20] | Experimental study (Colorectal Cancer) | CRC cell lines (SW480, SW620 tumorspheres) | OXPHOS pathway<br><br>Dysregulation of OXPHOS pathway genes (KEGG); altered mitochondrial mass & cardiolipin (membrane integrity); changes in ETC proteins (e.g., COX4I1) | OXPHOS gene signature associated with oxaliplatin resistance; altered mitochondrial function in tumorspheres. | OXPHOS gene signature as predictive biomarker, targeting mitochondrial metabolism overcome oxaliplatin resistance |
| **Wu et al., 2021** [21] | Experimental study (in vitro and in vivo)<br><br>(colorectal cancer) | Human CRC or fibroblasts (HCT116, 293T, MEFs, SW48, HT29)<br><br>Mice:<br>n = 11–12 per group (AOM/DSS model) | OXPHOS pathway<br><br>OXPHOS complex activity, mitochondrial protein interactions, Mitochondrial protease (OMA1) role in tumorigenesis, inflammation, Tumor growth | OMA1 deletion impaired mitochondrial dynamics, altered ECAR and ATP production, increased ROS, affected colorectal tumor | Targeting OMA1-OPA1 axis or HIF-1α-mediated glycolysis may reduce colorectal tumor growth |
| **Wang et al., 2022** [22] | In vitro validation (Colorectal cancer) | n=417 COAD patients<br><br>Cell lines: (Caco-2, HT-29, HCT-116, FHC) | OXPHOS pathway<br><br>OXPHOS-related genes (ORGs); mitochondrial oxidative phosphorylation pathways; Tumor microenvironment | High-risk patients based on ORG signature had distinct gene expression, altered immune infiltration, differences in TMB/MSI, and poorer overall survival | Potential targeting of OXPHOS pathways as therapeutic strategy |
| **Guo et al., 2023** [23] | Experimental study (Colorectal cancer) | CRC patients (n = 432 + 1,015);<br><br>Multiregional tumor samples (13 patients);<br><br>CRC cell lines ((DLD1, HT29) + normal (HIEC)) | mtDNA mutations<br><br>Altered mtDNA content (biogenesis changes), Dysregulation of mitochondrial proteins or in mitochondrial coding regions (MT-ND1 Complex I) | High mtDNA mutation burden in CRC; Mutations linked to mitochondrial reprogramming; Altered mtDNA content correlates with tumor progression. | mtDNA as biomarker; OXPHOS-targeted therapy. |
| **Gadicherla et al., 2024** [24] | Observational study (Colorectal Cancer) | n=25 colorectal cancer patients<br><br>(paired tumor vs non-tumor) | mtDNA mutations<br><br>In ETC complexes (I, IV, V) leads structural defects & OXPHOS impairment | Increase in mtDNA mutations in tumors; and mitochondrial dysfunction which increase progression | mtDNA biomarkers; OXPHOS-targeted therapy |
| **Chen et al., 2024** [25] | Observational cohort study (Colorectal Cancer) | n = 308 patients<br><br>CRC patients (Stage II, Stage III), tumor tissues with deficient mismatch repair (dMMR) | mtDNA mutations<br><br>Altered mtDNA copy number (mtDNA-CN) due to mitochondrial biogenesis changes and OXPHOS regulation | mtDNA-CN differs between tumor and non-tumor tissues; associated with prognosis (DFS, OS) in dMMR CRC | mtDNA-CN as prognostic biomarker; may guide response to chemotherapy (ACT, mFOLFOX6) |

*BC=breast cancer, CRC=colorectal cancer, TNBC=triple-negative breast cancer= PDX, patient-derived xenograft, OXPHOS= oxidative phosphorylation, mtDNA=mitochondrial DNA; ETC=electron transport chain, ROS=reactive oxygen species, OCR=oxygen consumption rate, ECAR= extracellular acidification rate, EMT=epithelial–mesenchymal transition, ALP= alkaline phosphatase, OPN= osteopontin, BMP2= bone morphogenetic protein 2, RUNX2= runt-related transcription factor 2, E-cad=E-cadherin, N-cad= N-cadherin, COAD=colon adenocarcinoma, TME=tumor microenvironment, ORGs= OXPHOS-related genes, TMB=tumor mutational burden, MSI= microsatellite instability, dMMR=deficient mismatch repair, mtDNA-CN= mitochondrial DNA copy number, ACT= adjuvant chemotherapy, mFOLFOX6=modified fluorouracil, leucovorin, and oxaliplatin regimen.*

In the 12 studies reviewed, clinical and experimental data all pointed to mitochondrial dysfunction as a key mechanism of tumor development due to mitochondrial dysfunction through mitochondrial DNA (mtDNA) mutations and oxidative phosphorylation (OXPHOS) reprogramming. The OXPHOS reprogramming in breast cancer was closely linked to tumor growth, metabolic adaptation as well as resistance to therapy, especially in triple-negative breast cancer (where OXPHOS inhibition decreased tumor progression and metabolic weaknesses were unveiled). Moreover, aggressive phenotypes, impaired electron transport chain (ETC) activity, and poor prognosis were associated with mtDNA mutations and changes in the copy number of the mitochondrial genome, and dysregulated mitochondrial dynamics and reactive oxygen species (ROS) further encouraged the proliferation, invasion and survival. Likewise, the burden of mutagenesis in the mitochondrial DNA, coupled with OXPHOS dysregulation, also played a role in metabolic reprogramming, tumor heterogeneity and resistance to therapy in colorectal cancer. The OXPHOS-related gene signatures were related to the poor clinical outcomes and immune microenvironment alterations, and pathways, including the OMA1-OPA1 axis, were involved in the regulation of hypoxia-dependent tumor growth. All these changes enhanced ROS, impaired ATP synthesis, and tumor-stimulating pathways, demonstrating the importance of mitochondrial mechanisms as significant therapeutic actions, and approaches involve the inhibition of OXPHOS and the regulation of mitochondrial dynamics and the use of mitochondrial DNA in prognosis and individual treatment.

The Newcastle Ottawa Scale (NOS) and Joanna Briggs Institute (JBI) Checklist of observational studies, ROBINS-I of clinical studies, a modified tool used in in vitro research, and SYRCLE of animal studies were used to assess the risk of bias. In general, the potential risk of bias was moderate. Low risk occurred in observational studies because of definitive populations and conventional methods, whereas medium risk occurred in experimental and preclinical studies because of the absence of sufficient randomization, absence of blinding, and insufficient justification of adequate sample size. Regardless of these shortcomings, there have been consistent findings on the evidence across studies that would be used in support of reliability. The overall certainty of evidence, assessed using the GRADE framework, was low as shown in Figure 2.

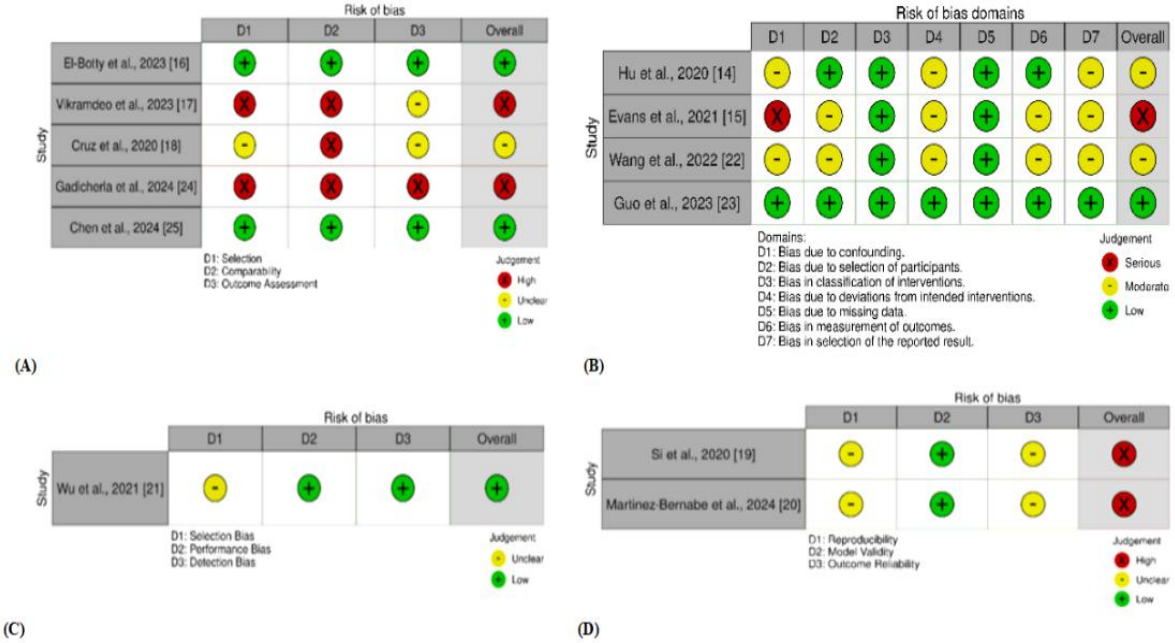


*Figure 2: Traffic plots for evaluating Risk of Bias Assessment. (2A) Cohort & Observational Studies Using Newcastle-Ottawa Scale (NOS) + JBI Checklist. (2B) Clinical + Translational Studies Using ROBINS-I (2C). In Vitro Studies Using Modified In Vitro Risk of Bias Tool. (2D) Experimental Studies (In Vivo + In Vitro) Using SYRCLE Risk of Bias Tool*

## Discussion

The current systematic review indicates that the core interconnected pathways that are involved in tumor progression in breast and colorectal cancer are mitochondrial DNA (mtDNA) mutations and oxidative phosphorylation (OXPHOS) reprogramming. In the surveys of the studies in the study, there appeared a common pathway whereby the alterations of the mtDNA, like, increased mutation load, loss of copy number and loss of mitochondrial-encoded gene, led to the structural and functional damage of the electron transport chain (ETC), especially complexes I, IV and V [26,27]. It was a dysfunction which was extensively associated with OXPHOS reprogramming, which leads to a change in ATP production, reactive oxygen species (ROS), and metabolic flexibility that facilitates tumor survival during stressful conditions (hypoxia and exposure to chemotherapy, among others) [28,29]. OXPHOS dependency seems to be a metabolic vulnerability in breast cancer, especially triple-negative variants, because its inhibition lowered tumor growth and boosted sensitivity to therapy [30]. On the same note, OXPHOS-associated gene signatures and modifications in the number of copies of the mitochondrial DNA were found to have a strong correlation with prognosis, changes in immune microenvironment, and resistance to treatment in colorectal cancer including oxaliplatin [31,32]. All these findings support the idea that mitochondrial bioenergetics is not a passive observer but its driver, which has an impact on the proliferation, invasion, metastasis, and resistance to treatment [33].

These findings are well correlated with the available literature that defines cancer metabolism as being highly tuned and not limited to glycolysis as was conventionally explained by the Warburg effect [35]. Recent research has given more emphasis on the

co-existence of glycolytic and oxidative metabolic phenotypes and tumours switch according to the environmental and therapeutic pressures [37,38]. These results are in accordance with the reports that OXPHOS has a significant role in the maintenance of cancer stem cells, metastatic ability, and drug resistance in various cancer types [39]. In addition, the reported correlation between the presence of the mutations in the mitochondrial DNA and the altered functioning of mitochondria is in agreement with the general based genomic research involving the fact that mitochondrial genomic instability is one of the determinants of tumor heterogeneity and disease evolution [40]. Recent publications on the pathways discovered including the OMA1-OPA1 axis and the involvement of proteins of mitochondrial dynamics (e.g. MFN1, DRP1) also help confirm new evidence that mitochondrial structure-function interactions are part of cancer biology [36]. Notably, the implications of the identified therapeutic strategies, including OXPHOS targeting, mitochondrial dynamics regulation, and the use of the mitochondrial-targeted therapies, are consistent with the current translational research efforts and clinical trials aimed at understanding the clinical applicability of the identified findings [34].

In spite of these advantages, it should be noted that this systematic review has a number of limitations. First, heterogeneous types of study designs provided, including in vitro experiments and observational clinical studies, can lead to variability and consequently to the possibility that such results will not be comparable. Second, the conclusions may not be generalizable especially when the study sample is very limited as in the case of the number of included studies and this is especially true in instances where subgroup analysis is to be made between the breast and colorectal cancers. Third, it is not possible to rule out potential publication bias, because the studies were more likely to be published, which had significant findings. Also, the absence of meta-analysis in the heterogeneity of the results and methodologies used does not allow quantify the effect sizes and makes more conclusive conclusions. The differences of the reporting standards used in the studies were also an obstacle in the data synthesis and interpretation.

The gaps highlighted by future research studies must fill these gaps by undertaking large-scale, well-designed clinical studies to support the role of the use of mtDNA mutations and OXPHOS reprogramming as diagnostic, prognostic, and treatment assumptions. To enhance reproducibility and comparability, standardization of procedures to measure mitochondrial function and genetic changes is needed. Also, further studies on the interplay of mitochondrial metabolism and tumor microenvironment such as immune modulation can offer more insights into cancer progression. The future of therapeutic and clinical assessment of mitochondrial-targeted therapies, especially in conjunction with the current treatment modalities, is a valid direction toward better patient outcomes. Lastly, the combination of multi-omics protocols, such as genomic, transcriptomic, and metabolomic techniques, might contribute to improving the knowledge about mitochondrial reprogramming and assist in the development of individualized cancer treatment.

## Conclusion

This is a systematic review that has brought to the fore the presence of mitochondrial DNA mutations and oxidative phosphorylation reprogramming as being a critical factor in the progression of breast and colorectal cancers. These changes impair the work of the electron transport chain, increase the production of reactive oxygen species, and increase metabolic plasticity, which leads to the development of tumor growth, metastasis, and resistance to treatment. The commonality of results in the literature that has been carried out substantiates the possibility of mitochondrial pathways as effective treatment targets.

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