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Polyphenol-based antioxidant strategies for personalized prevention of hereditary cancer

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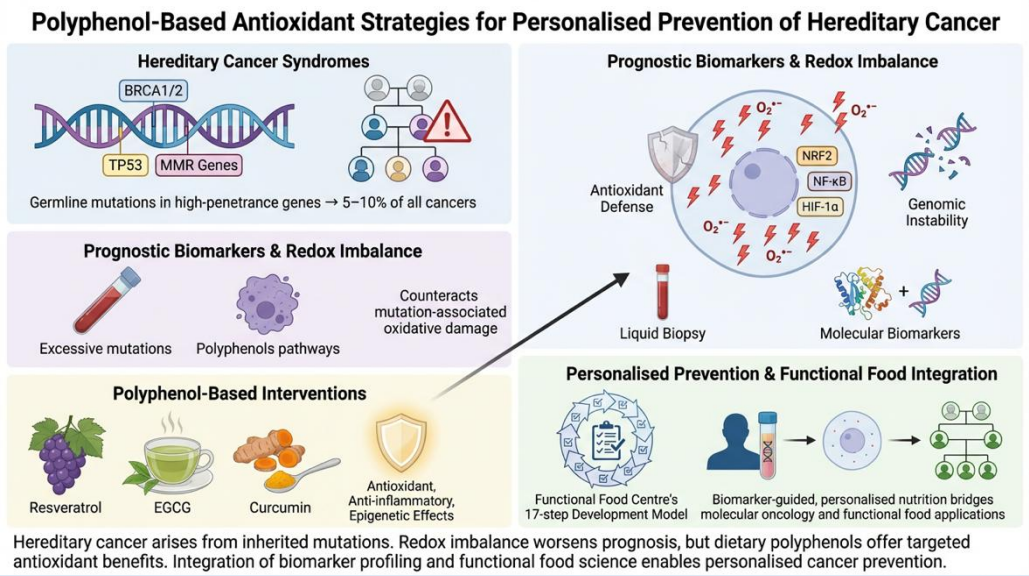
ABSTRACT

Hereditary cancer syndromes, accounting for approximately 5–10% of all malignancies, are caused by germline mutations in high-penetrance genes such as BRCA1/2, TP53, and mismatch repair genes, leading to an increased risk of early-onset and aggressive cancers. Accurate prognostic biomarkers are essential for risk stratification and personalized prevention in individuals with genetic predisposition.

This review focuses on the prognostic relevance of oxidative stress and redox-dependent mechanisms in hereditary cancers. Redox imbalance, characterized by excessive reactive oxygen species (ROS) and impaired antioxidant defense, promotes genomic instability, tumor progression, and therapy resistance. Key redox-sensitive pathways, including transcription factors nuclear factor erythroid 2–related factor 2 (NRF2), nuclear factor-κB (NF-κB), and hypoxia-inducible factor-1α (HIF-1α), are discussed alongside emerging molecular and liquid biopsy biomarkers. Importantly, several dietary polyphenols, such as resveratrol, epigallocatechin gallate (EGCG), and curcumin, exhibit antioxidant, anti-inflammatory, and epigenetic effects that may help counteract mutation-associated oxidative damage. Integrating prognostic biomarker profiling with polyphenol-based, biomarker-guided functional food strategies represents a promising, non-invasive approach to personalized prevention in hereditary cancer.

Novelty of Study: This review is novel in that it integrates oxidative-stress–related prognostic biomarkers with polyphenol-based dietary interventions within the structured framework of functional food science, specifically applying the Functional Food Centre's 17-step development model to hereditary cancer prevention, thereby proposing a biomarker-guided, personalized nutrition strategy that bridges molecular oncology and functional food applications.

Keywords: Hereditary cancer syndromes; Prognostic biomarkers; Oxidative stress; Redox signaling; dietary polyphenols; Personalized cancer prevention; Functional food science



Graphical Abstract: Polyphenol-Based Antioxidant Strategies for Personalized Prevention of Hereditary Cancer

INTRODUCTION

Cancer remains a leading cause of morbidity and mortality worldwide [1]. In 2020, there were 18.1 million cancer cases globally, including 9.3 million among men and 8.8 million among women. The burden of disease continues to increase. According to the National Centre for Disease Control and Public Health of Georgia, malignant tumors are among the leading causes of morbidity in the country, and the number of newly diagnosed cases increased between 2003 and 2021 [2-3].

While environmental and lifestyle factors significantly contribute to carcinogenesis, approximately 5–10% of all cancers are linked to inherited genetic mutations that markedly increase lifetime cancer risk [4-5]. Hereditary cancer syndromes, such as Hereditary Breast and Ovarian Cancer (HBOC) syndrome, Lynch syndrome, and Li-Fraumeni syndrome, are characterized by germline mutations in high-penetrance genes involved in DNA repair, cell-cycle regulation, and apoptosis [6-7].

In this high-risk population, the identification and interpretation of oncological biomarkers—biological molecules that indicate tumor presence, progression, or therapeutic response—are crucial for clinical decision-making [8–16]. In particular, prognostic biomarkers provide essential information about the likely course of disease, irrespective of therapy, enabling clinicians to stratify patients by risk and tailor surveillance or intervention strategies accordingly. Among patients with

hereditary predisposition, tumor biomarkers such as CA-125, PSA, CEA, CA 19-9, and emerging molecular and genomic markers are being investigated for their potential to predict disease progression, recurrence, and overall survival [17–19].

While some biomarkers have demonstrated robust prognostic value in sporadic cancers, their effectiveness in hereditary cancer syndromes remains less well established. This is complicated by variations in tumor biology, age of onset, and penetrance. For instance, breast cancers associated with *BRCA1* mutations commonly exhibit triple-negative characteristics and are biologically aggressive, which alters the prognostic significance of traditional markers such as Ki-67 and estrogen/progesterone receptor status [20]. Similarly, mismatch-repair (MMR) deficiency in colorectal cancers linked to Lynch syndrome is associated with unique immunological profiles that affect both prognosis and therapeutic response [21].

As the global burden of cancer continues to rise, improving prevention and early intervention remains a major public-health priority. Alongside genetic screening and biomarker-guided surveillance, lifestyle interventions—particularly dietary modification—are increasingly recognized as modifiable factors that may influence cancer incidence and progression, even in genetically predisposed individuals. Emerging evidence suggests that diets rich in natural polyphenols, including flavonoids, phenolic acids, and stilbenes derived from fruits, vegetables, green tea, and whole grains, exhibit chemopreventive and functional food-related properties through antioxidant, anti-inflammatory, and epigenetic mechanisms [22–26]. Polyphenols have been shown to modulate key signaling pathways involved in carcinogenesis, including PI3K/Akt, NF-κB, and Wnt/β-catenin, while also suppressing oncogene expression and promoting tumor-suppressor activity [27].

From the perspective of functional food science, these compounds may also be considered as food-derived bioactive compounds with potential applications in reducing disease risk and promoting health [25-29]. In this context, the development of preventive nutritional strategies requires a structured framework that links bioactive compounds with measurable health outcomes. The Functional Food Centre (FFC) has proposed a 17-step functional food development framework to guide the translation of bioactive compound research into clinically relevant functional foods. This framework includes identification of bioactive compounds, characterization of biological mechanisms, biomarker validation, dose–response assessment, safety evaluation, and clinical testing before responsible translation into dietary recommendations [30–33]. Integrating polyphenol-based prevention strategies within this structured framework may help bridge the gap between experimental evidence on phenolic compounds and practical nutritional interventions to reduce hereditary cancer risk.

Within the framework of functional food science, polyphenols should not be viewed solely as isolated phytochemicals but also as food-derived bioactive compounds that may contribute to disease-risk reduction when delivered through evidence-based functional foods. This perspective is especially relevant to hereditary cancer prevention, where foods enriched in phenolic compounds may help modulate oxidative stress, inflammation, and redox-sensitive signaling pathways associated with inherited cancer susceptibility. Recent publications further support the importance of integrating food bioactive compounds, functional foods, and biomarker-oriented prevention strategies in chronic disease research, including cancer prevention and management [29-33].

Individuals with *BRCA* mutations may particularly benefit from dietary strategies that help combat oxidative DNA damage and promote genomic stability. For instance, resveratrol and epigallocatechin-3-gallate (EGCG), two well-studied polyphenols, have

demonstrated protective effects in *BRCA1/2*-deficient cells [33-34]. Furthermore, combining polyphenol-rich diets with regular biomarker monitoring may represent a promising complement to current clinical strategies for managing hereditary cancer risk.

This review examines the roles of oxidative stress mechanisms, prognostic biomarkers, and dietary polyphenols in the prevention of hereditary cancers. Emphasis is placed on redox regulation, oxidative DNA damage, and redox-sensitive molecular signaling pathways that contribute to tumor initiation and progression in genetically predisposed individuals. The review also highlights the emerging relevance of biomarker-guided nutritional strategies, in which dietary polyphenols may modulate oxidative stress, inflammation, and epigenetic regulation associated with hereditary cancer susceptibility. Within the framework of functional food science, these compounds are discussed as potential bioactive ingredients in functional foods designed to support personalized prevention strategies. By integrating molecular biomarkers with dietary interventions, polyphenol-based approaches may complement existing clinical surveillance and risk-reduction strategies for individuals carrying high-penetrance germline mutations.

Genetic Predisposition, Oxidative Stress, and Prognostic Biomarkers in Hereditary Cancers: Hereditary cancer syndromes constitute a biologically distinct group of malignancies characterized by early onset, bilateral or multifocal tumors, and familial clustering across generations. Understanding the genetic and redox-related mechanisms underlying these cancers is essential for accurate risk assessment, prognostication, and personalized management.

Malignant neoplasms arise from irreversible genetic damage affecting either germline or somatic cells, rendering these cells increasingly vulnerable to environmental carcinogens and capable of malignant transformation. These carcinogenic factors include both inherited and acquired influences, such as age, sex, ionizing radiation, obesity, and exposure to environmental toxins.

Approximately 5–10% of all cancers are attributable to hereditary genetic mutations [35]. To date, over 500 mutations in somatic or germ cells have been identified, many of which disrupt regulatory mechanisms that maintain genomic stability, control cell proliferation, or prevent apoptosis. Of these, mutations in approximately 100 genes have been identified in human germline DNA, making them heritable and significantly increasing the risk of cancer [30]. In families with a history of prostate or breast cancer, the likelihood of developing tumors of the same type in subsequent generations may reach 30–40% [36-37]. This familial aggregation likely reflects a synergistic interplay between inherited genetic defects and shared environmental exposures [38].

Hereditary cancers are frequently characterized by distinct clinical features, including early onset, aggressive histological subtypes, unique molecular profiles, and variable responses to treatment, all of which underscore the importance of tailored prognostic assessment in genetically predisposed individuals.

Genetic and Oxidative Mechanisms in Tumorigenesis: The molecular pathogenesis of cancer is complex and multifactorial. A key contributor is dysregulation of redox homeostasis, reflecting an imbalance between ROS and antioxidant defense systems. ROS—including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH)—are by-products of aerobic metabolism and cellular stress [11, 39–42]. At physiological levels, they function as second messengers in intracellular signaling pathways, but at excessive levels, they promote DNA damage, gene mutations, chromosomal instability, and activation of oncogenic pathways [43].

Accumulating evidence suggests that mitochondrial dysfunction acts both as a source and a target of ROS in

cancer cells. Mutations in mitochondrial DNA (mtDNA), particularly in genes encoding components of the electron transport chain, can increase ROS production and are increasingly recognized as early events in tumorigenesis. These mitochondrial alterations not only amplify oxidative damage but also reprogram cellular metabolism towards aerobic glycolysis (the Warburg effect), thereby reinforcing the oncogenic phenotype [44-45].

Oxidative stress disrupts the redox-sensitive control of tumor suppressor genes and oncogenes, contributing to tumor initiation and progression. To counteract ROS, cells deploy antioxidant defense systems, including enzymatic components such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX), as well as non-enzymatic molecules such as glutathione, vitamins A, C, and E, and flavonoids [43, 46]. These systems neutralize ROS and prevent their accumulation, thereby maintaining redox homeostasis.

Under conditions of persistent oxidative stress, tumor cells undergo metabolic and genetic reprogramming that facilitates adaptation to the hostile tumor microenvironment. This process involves sustained activation of redox-sensitive transcription factors, including nuclear factor erythroid 2–related factor 2 (NRF2), hypoxia-inducible factor-1α (HIF-1α), and NF-κB. Activation of these pathways alters gene-expression profiles that promote proliferation, angiogenesis, and evasion of apoptosis [47–49].

Chronic hyperactivation of NRF2, often associated with somatic mutations in the Kelch-like ECH-associated protein 1 (KEAP1), plays a crucial role in the cellular response to oxidative stress. NRF2 is a key regulator of the antioxidant response by activating cytoprotective genes that enable cells to withstand oxidative and inflammatory stress. This hyperactivation provides cancer cells with a survival advantage by enhancing antioxidant capacity, increasing drug resistance, and promoting metastatic potential [50-51].

Ultimately, redox imbalance contributes to the accumulation of oncogenic mutations, enhances cancer-cell survival under hypoxic and inflammatory conditions, and supports the selective processes that drive malignant transformation [52] (Figure 1).

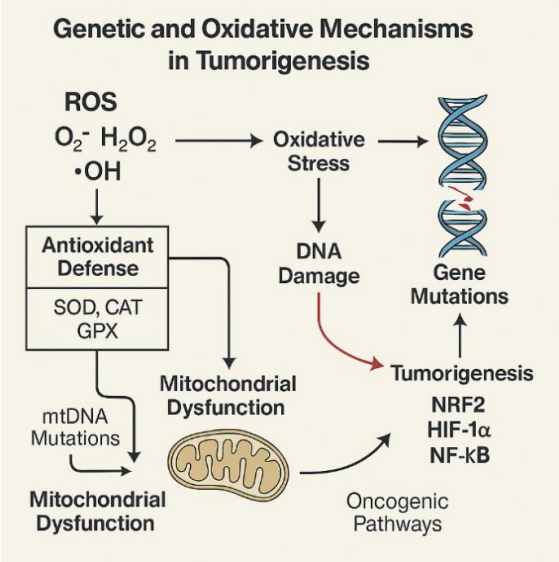


Figure 1. Genetic and oxidative mechanisms in tumorigenesis.

Recent integrative multi-omics studies suggest that redox imbalance may be associated with specific mutational signatures, epigenetic alterations, and immune-evasion mechanisms in several hereditary

cancers, including *BRCA1/2*-associated cancers and Lynch syndrome. These findings indicate that redox biomarkers may have value not only for prognostication but also for stratifying patients for redox-targeted therapies in precision oncology [53-54].

Table 1 summarizes key prognostic biomarkers associated with hereditary cancers and their mechanisms of action. These data highlight important clinical implications for risk stratification and early detection through genetic testing for germline mutations in high-penetrance genes such as *BRCA1, BRCA2, TP53*, and *MLH1*.

Table 1. Key Prognostic Biomarkers in Hereditary Cancer.

Cancer Syndrome	Gene(s) Involved	Prognostic Biomarkers	Mechanism	Clinical Implication
HBOC (Breast/Ovarian)	*BRCA1, BRCA2*	CA-125, HE4, Ki-67, p53, ctDNA [55-56]	HR deficiency, oxidative stress imbalance [55-56]	Predicts recurrence, PARP inhibitor sensitivity [55]
Lynch Syndrome	*MLH1, MSH2, MSH6, PMS2*	MSI, MMR status, CD8+ TILs, BRAF V600E [55]	DNA mismatch repair failure, immune activation [55]	Prognosis and immunotherapy response [55]
Li-Fraumeni Syndrome	*TP53*	p53 overexpression, ctDNA, oxidative stress markers [56, 57]	p53 dysfunction, redox imbalance [57]	Surveillance and early detection [55-56, 58]
Familial Colorectal Cancer	*APC, MUTYH, MLH1*	MSI, 8-oxodG, antioxidant enzyme levels [57-58]	Oxidative DNA damage, MMR loss [57, 59]	Tumor progression and therapy response [57-58]
General Hereditary Risk	Various	ROS, GSH/GSSG ratio, SOD/GPX levels, hemorheological data [26, 59]	Redox dysregulation, altered blood rheology [59]	Risk stratification, prognosis, treatment guidance [52, 60]

Redox Adaptation in Tumor Cells: Tumor cells exhibit a high degree of redox-adaptability. Cancer cells display a distinct redox profile characterized by increased ROS production and enhanced antioxidant capacity, which supports survival under oxidative stress. Sources of ROS in tumors include mitochondrial electron transport chain dysfunction, oncogene activation (e.g., MYC and RAS), hypoxia-induced mitochondrial remodeling, and infiltration of inflammatory cells [61].

Additionally, reduced antioxidant expression or post-translational modifications of antioxidant enzymes, such as the SOD acetylation in many types of cancer cells [62], have been shown to alter their catalytic efficiency and localization, potentially shifting their function from antioxidant to pro-oxidant, which may paradoxically confer further redox destabilization [43, 63-65]. Moreover, tumor-associated immune cells, such as neutrophils and macrophages, contribute to ROS generation in the tumor microenvironment, exacerbating oxidative stress.

While excessive ROS levels can lead to cytotoxicity, they are also vital for cellular signaling and play a crucial role in coordinating cellular signaling. High ROS levels may induce senescence or apoptosis; however, tumor cells circumvent these effects by reprogramming transcriptional regulators and altering metabolism to produce antioxidants, such as glutathione and the thioredoxin system. NRF2, a key regulator of the antioxidant response, is often persistently active in cancer cells due to mutations in *KEAP1* or indirectly through oncogenic pathways [66–68] (Figure 2).

Emerging data suggest that mitochondrial ROS serve as essential mediators in the maintenance of cancer stem cells and in epithelial–mesenchymal transition (EMT), both of which are critical for metastasis and treatment resistance. Specifically, mitochondrial ROS have been shown to activate the Wnt/β-catenin and Notch signaling pathways, thereby enhancing stemness and tumor-initiating capacity [69-70].

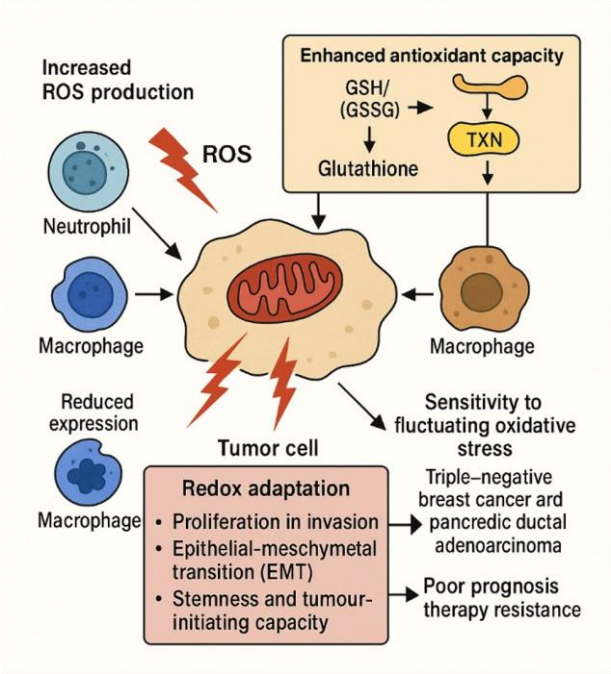


Figure 2. Redox-adaptation in tumor cells.

Tumor cells exploit this duality by maintaining a pro-survival redox state that facilitates proliferation and invasion while evading apoptosis [52, 68]. The high redox plasticity of tumor cells allows them to tolerate fluctuating oxidative pressures during metastasis and immune surveillance. This adaptation supports tumor progression and is associated with poor prognosis and therapy resistance, particularly in cancers such as triple-negative breast cancer and pancreatic ductal adenocarcinoma [71].

Furthermore, single-cell transcriptomic analyses have revealed substantial intratumoral heterogeneity in redox responses. Distinct tumor-cell subpopulations exhibit differential NRF2 pathway activity and antioxidant profiles, which may contribute to heterogeneous therapeutic responses and clonal evolution under treatment pressure [72].

Targeting redox-adaptation mechanisms, therefore, represents a promising therapeutic strategy, particularly for tumors with germline mutations in DNA repair and oxidative stress regulatory genes. Preclinical studies are increasingly focusing on synthetic-lethality approaches that exploit redox vulnerabilities in BRCA1/2- or ATM-deficient tumors. These strategies involve using ROS-inducing agents in combination with inhibitors of the thioredoxin or glutathione systems and may selectively target redox-adapted cancer cells while preserving normal tissue [73-74].

Tumor Suppressor Genes and Oxidative Stress Regulation: Tumor suppressor genes such as *TP53, BRCA1*, and *BRCA2* play essential roles in maintaining genomic integrity by regulating cell-cycle checkpoints, DNA repair, and apoptosis [52, 75]. Emerging evidence suggests that these genes also influence the oxidative stress response by affecting the expression of detoxifying enzymes and ROS scavengers [77-79]. These regulatory mechanisms are linked to the antioxidant response, as they increase the expression of several detoxification-related genes, including glutathione S-transferases (GSTs), while reducing intracellular ROS levels [55, 80-81].

Loss-of-function mutations in *BRCA1* or *BRCA2* impair homologous recombination (HR), reduce

antioxidant-gene expression, and lead to the accumulation of ROS. This accumulation promotes genomic instability and tumor initiation, thereby increasing metabolic stress and further exacerbating ROS-mediated damage [56, 80].

Recent studies have demonstrated that *BRCA1* deficiency leads to dysregulated mitochondrial dynamics, characterized by increased mitochondrial fragmentation and reduced mitophagy, thereby amplifying intracellular ROS production and compromising cellular energy homeostasis [81-82]. Moreover, *BRCA1* and *BRCA2* have been shown to interact with NRF2, further linking *BRCA* mutations to impaired antioxidant defense [83].

Germline mutations in *BRCA1/2* account for 5–10% of hereditary breast and ovarian cancers and are also implicated in prostate, pancreatic, and colorectal cancers. The clinical penetrance of these mutations depends on the specific variant, its location, its impact on protein function, and interactions with hormonal and environmental exposures [66]. The oxidative stress–DNA damage–tumorigenesis axis is particularly relevant in *BRCA*-deficient tumors, where targeted therapies such as poly (ADP-ribose) polymerase (PARP) inhibitors exploit synthetic lethality arising from homologous recombination failure [85].

Moreover, emerging clinical evidence indicates that *BRCA1/2*-mutated tumors exhibit increased immunogenicity, characterized by higher levels of tumor-infiltrating lymphocytes (TILs) and elevated tumor mutational burden (TMB), which may render them more responsive to immune-checkpoint inhibitors [83–85]. These findings support ongoing evaluation of combined strategies that incorporate PARP inhibition and immunotherapy to improve outcomes in BRCA-related malignancies [87].

High-risk mutations in BRCA genes impair error-free homologous DNA repair and significantly increase the risk of developing breast, ovarian, and certain other cancers. The cancer risk associated with a mutation depends on the specific type and location of the variant, as well as additional exogenous and endogenous factors.

Hemorheological Changes in Cancer Progression: In patients with cancer, significant changes in blood flow and clotting are often observed, even in the absence of overt thrombosis. Cancer is associated with a prothrombotic state characterized by hypercoagulability, increased platelet aggregation, and impaired microcirculatory blood flow [8, 10, 12-13, 88-89]. These changes are often especially pronounced in the early stages of disease.

This hypercoagulable state is primarily driven by factors released from tumors, including tissue factors, cancer procoagulants, and inflammatory cytokines. These substances activate the coagulation cascade and platelets, resulting in increased thrombin production and fibrin deposition [90].

Research has shown correlations between hemorheological and hemostatic indicators in cancer patients. These include high platelet-aggregation activity, reduced hematocrit, increased erythrocyte aggregation, and elevated plasma viscosity. Such changes reduce the efficiency of oxygen transport, leading to microcirculatory hypoxia, which contributes to thrombus formation, tumor progression, and metastasis [61, 91].

Additionally, elevated plasma fibrinogen levels and increased blood viscosity are linked to poorer clinical outcomes in various cancers. These factors reflect systemic inflammation and support tumor-cell survival and dissemination [92-93].

Recent evidence suggests that the cancer-associated prothrombotic state is further amplified by immunothrombosis. In this process, activated neutrophils release neutrophil extracellular traps (NETs), which are web-like structures composed of chromatin enriched with histones and proteolytic enzymes. These NETs act as scaffolds for platelet adhesion and fibrin deposition [94-96]. NETs not only promote thrombosis

but also facilitate cancer progression by trapping circulating tumor cells, protecting them from immune clearance, and enhancing metastatic potential [97]. Elevated levels of circulating NETs have been observed in several malignancies and correlate with advanced disease stage and poorer prognosis.

These changes contribute to tumor progression and metastasis, as impaired oxygen delivery caused by erythrocyte aggregation and plasma hyperviscosity exacerbates hypoxia. Hypoxia is a known trigger for angiogenesis and EMT [91]. Stabilization of HIF-1α under these conditions leads to increased levels of vascular endothelial growth factor (VEGF), which promotes neovascularization—a process crucial for tumor growth and metastatic potential [96]. Additionally, coagulation factors can interact with tumor cells and the tumor microenvironment, aiding in the formation of metastatic niches. While many of these changes are nonspecific, in certain cancer types, their extent correlates with tumor stage and prognosis. This suggests a potential prognostic role for hemostatic and rheological biomarkers in oncology.

Rheological and coagulation changes commonly observed in cancer patients, especially those with inherited predispositions, may not only reflect tumor burden but also contribute directly to disease progression and metastasis through mechanisms such as microvascular dysfunction and hypoxia-driven signaling [91, 97–101]. Emerging evidence suggests that inherited thrombophilia mutations, such as Factor V Leiden or prothrombin G20210A, may exacerbate these rheological and coagulation abnormalities, thereby further influencing cancer progression and increasing the risk of thrombotic complications [101].

These findings support the need to incorporate thromboprophylaxis strategies and therapies targeting NETs, such as DNase treatment or PAD4 inhibitors, into the management of high-risk cancer patients, particularly those with hereditary cancer syndromes [101-102]. This underscores the importance of a comprehensive assessment of coagulation and hemorheology in individuals with hereditary cancer syndromes.

Potential of Dietary Polyphenols as a Complementary Approach to Biomarker-Guided Precision Prevention in Hereditary Cancer: Hereditary cancer syndromes such as HBOC and Lynch syndrome are driven by germline mutations in high-penetrance genes involved in DNA repair, cell-cycle regulation, and apoptosis. In this context, integrating functional food science into hereditary cancer prevention is increasingly relevant, as food-derived bioactive compounds may influence oxidative stress, inflammatory status, and molecular biomarkers associated with tumor initiation and progression. Prognostic assessment of redox-balance indicators and hemorheological parameters (e.g., plasma viscosity and platelet aggregation) may help identify patients with aggressive disease phenotypes, particularly in early-stage cancers associated with inherited predisposition.

Recent data suggest that elevated oxidative-stress markers, such as malondialdehyde (MDA) and 8-hydroxy-2’-deoxyguanosine (8-OHdG), correlate with higher tumor grade and poorer survival in *BRCA1/2*- and *MMR*-deficient cancers, supporting their potential prognostic utility [81, 101]. Additionally, dysregulated antioxidant enzyme activities, including decreased superoxide dismutase, catalase, and glutathione peroxidase, have been observed in germline mutation carriers even before clinical manifestation of malignancy, indicating that redox profiling may aid in preclinical risk stratification [102].

Therapeutic strategies targeting redox pathways may benefit *BRCA*- or *TP53*-mutant tumors, which are particularly sensitive to redox imbalance. Lifestyle and dietary interventions aimed at modulating oxidative

stress may therefore serve as adjunctive approaches in carriers of high-risk mutations. There is growing interest in integrative preventive strategies involving food-derived bioactive compounds**.** Among these, polyphenols—a diverse group of plant-derived secondary metabolites—have garnered considerable attention for their antioxidant, anti-inflammatory, and epigenetic-modulating properties, which may be especially relevant in genetically predisposed individuals [103–110].

Polyphenols are broadly classified into flavonoids, phenolic acids, lignans, and stilbenes, with notable examples including quercetin, resveratrol, curcumin, and EGCG. These compounds are abundant in fruits, vegetables, green tea, cocoa, and whole grains (Figure 3).

To effectively harness the biological activity of polyphenols in preventive health strategies, a systematic development process is essential from a functional food science perspective. According to the Functional Food Centre's 17-step framework for developing functional foods, it is crucial to identify bioactive compounds, characterize their mechanisms of action and validate their health benefits through biomarkers and clinical evidence before incorporating them into functional foods [30, 33].

In the context of hereditary cancer prevention, dietary polyphenols such as resveratrol, EGCG, curcumin, and quercetin meet several of these criteria. They have demonstrated antioxidant, anti-inflammatory, and epigenetic regulatory effects in preclinical and clinical studies [102, 112-113]. These properties support their potential role as ingredients in functional foods that target oxidative stress-related biomarkers and redox signaling pathways associated with inherited cancer susceptibility [28, 114-117]. This conceptual bridge is directly applicable to hereditary cancer, where the use of polyphenol-rich functional foods may complement surveillance strategies based on redox, inflammatory, and molecular biomarkers.

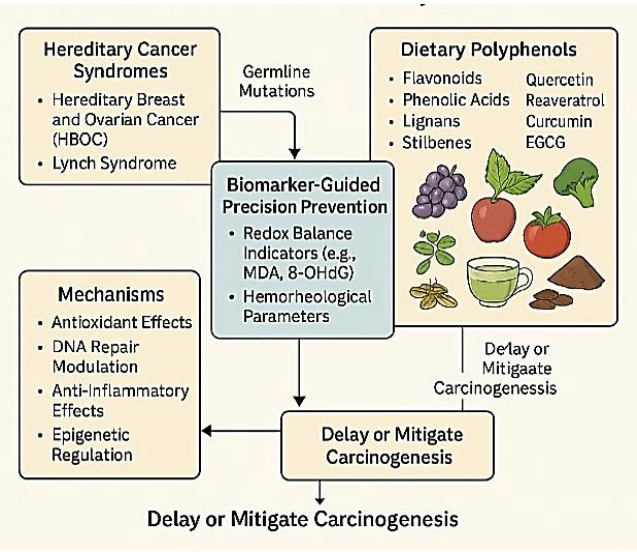


Figure 3. Potential of Dietary Polyphenols as a Complementary Approach to Biomarker-Guided Precision Prevention in Hereditary Cancer

Within the framework of functional food science, dietary polyphenols can be considered bioactive compounds with potential health benefits when consumed in effective and safe amounts as components of functional foods. Recent publications emphasize that functional foods should be supported by scientific evidence on their bioactive composition, safety, bioavailability, and measurable physiological effects, rather than by presumed health claims alone [114–117]. This perspective is particularly important for hereditary

cancer prevention, where polyphenol-rich foods may serve not only as sources of antioxidant and anti-inflammatory compounds, but also as candidates for biomarker-guided nutritional strategies targeting oxidative stress and redox imbalance.

Emerging studies suggest that polyphenols can also modulate the expression of DNA repair genes (e.g., *BRCA1, RAD51*, and *MLH1*) and enhance the efficacy of chemotherapeutic agents by sensitizing cancer cells to oxidative damage [29, 113]. For instance, resveratrol has been shown to restore *BRCA1* expression in triple-negative breast cancer models through promoter demethylation, while EGCG inhibits NF-κB signaling and reduces inflammation in MMR-deficient colorectal cancer cells [118-119].

Mechanistically, polyphenols modulate key cellular signaling pathways such as PI3K/Akt, MAPK, NF-κB, and Wnt/β-catenin, which are frequently dysregulated in tumor development [119-125]. The relevance of these compounds to hereditary cancer prevention is further strengthened by recent publications linking phenolic compounds, food bioactive compounds, functional foods, and modulation of cancer-related biomarkers [114-117]. Importantly, their ability to influence redox homeostasis [116-131] and DNA repair makes these compounds particularly attractive in hereditary cancers linked to impaired genome maintenance.

Table 2. Selected Dietary Polyphenols with Anticancer Properties and Potential Relevance to Hereditary Cancer.

Polyphenol	Natural Sources	Mechanisms of Anticancer Action	Relevance to Hereditary Cancer Syndromes	Ref.
Resveratrol	Grapes, red wine, berries	Antioxidant; induces apoptosis; inhibits PI3K/Akt and NF-κB signaling; modulates p53 and BRCA1 expression	Enhances DNA repair in BRCA-deficient cells; epigenetic modulation in breast cancer	[33-34]
Curcumin	Turmeric (*Curcuma longa*)	Anti-inflammatory; inhibits COX-2, STAT3, NF-κB; regulates miRNAs and DNA methylation	Upregulates MMR genes in Lynch syndrome models; reduces polyp burden in FAP	[131]
Epigallocatechin-3-gallate (EGCG)	Green tea	Induces apoptosis; inhibits angiogenesis; modulates Akt/mTOR and MAPK pathways	Suppresses tumor growth in BRCA1-deficient models; antioxidant protection of DNA	[119, 124]
Quercetin	Apples, onions, berries	Induces cell cycle arrest; modulates p53 and Bcl-2 family proteins; ROS scavenging	Reduces oxidative stress and inflammation; potential adjunct in colorectal cancer models	[132]
Genistein	Soy products	Inhibits tyrosine kinases; modulates estrogen receptors and epigenetic markers	Enhances BRCA1/2 gene expression; affects hormone-responsive hereditary breast cancers	[34, 131]
Apigenin	Parsley, chamomile, celery	Inhibits proliferation; induces autophagy and apoptosis; suppresses ERK and Wnt signaling	Antioxidant effects may benefit MMR-deficient cells; suppresses inflammation	[132]
Kaempferol	Kale, spinach, tea, citrus fruits	Induces apoptosis; inhibits angiogenesis; suppresses PI3K/Akt and ERK signaling	Limited direct evidence in hereditary models; enhances redox balance in general cancers	[31, 118]
Ellagic acid	Pomegranates, berries, and walnuts	Antioxidant; promotes DNA repair; inhibits cell proliferation and metastasis	May mitigate BRCA1-related DNA damage; potential preventive agent in hereditary breast CA	[22]
Polymethoxylated flavones	Citrus fruit peel, essential oils	Modulation of estrogen-related activity, cytochrome P450 enzymes, and aryl hydrocarbon receptor (AhR) signaling	May modulate multiple molecular targets and exert potential anticancer effects	[120, 122]

In *BRCA1/2*-mutated cells, which exhibit compromised homologous recombination repair, polyphenols such as resveratrol have been shown to reduce oxidative stress and enhance the expression of tumor suppressor genes, potentially attenuating malignant transformation [34, 131]. EGCG from green tea has similarly demonstrated chemopreventive effects by inhibiting proliferation and inducing apoptosis in *BRCA*-deficient breast cancer models, partly through modulation of the AKT and mTOR pathways [132]. Moreover, polyphenols exert epigenetic regulatory effects—such as inhibiting DNA methylation and modifying histone—which may help restore the expression of silenced tumor suppressor genes in precancerous lesions [133].

Additionally, combination treatments using polyphenols with PARP inhibitors have shown synergistic anticancer effects in *BRCA1*-deficient preclinical models, suggesting that dietary polyphenols may enhance the efficacy of targeted therapies by further exploiting redox imbalance and DNA repair vulnerabilities.

In Lynch syndrome, which is characterized by MMR deficiency and microsatellite instability, polyphenols may modulate the tumor microenvironment and immune surveillance. For example, curcumin has been reported to upregulate MMR-gene expression and suppress pro-inflammatory cytokines, thereby potentially influencing early neoplastic transformation in the colonic epithelium [134]. Furthermore, curcumin and quercetin have been evaluated in familial adenomatous polyposis (FAP), a model of hereditary colorectal cancer, and shown to reduce polyp number and size in small clinical studies [135], suggesting translational potential for related syndromes.

Emerging studies also highlight the role of polyphenols in modulating gut microbiota composition, which may be particularly relevant in colorectal cancer syndromes like Lynch and FAP. By promoting short-chain fatty acid (SCFA)-producing bacteria and reducing pathogenic taxa, polyphenols help maintain intestinal barrier function and reduce pro-carcinogenic inflammation [136-137].

Within the Functional Food Center's 17-step development framework, such mechanistic insights represent an early stage of functional food validation, where bioactive compounds are linked to specific biological targets and disease-related biomarkers. Subsequent stages involve optimizing bioactive dosage, assessing bioavailability, safety evaluations, and validating through human clinical studies [30-33, 115-118]. Applying this structured development pathway to polyphenol-rich foods may facilitate the translation of laboratory findings into clinically meaningful dietary strategies for individuals with hereditary cancer susceptibility.

The concept of biomarker-guided prevention aligns closely with the Functional Food Centre's structured approach to functional food development. Within the FFC 17-step framework, biomarkers play a central role in validating the physiological effects of bioactive compounds and assessing their efficacy in disease prevention [115-118]. In hereditary cancer syndromes, biomarkers such as oxidative-stress indicators (e.g., 8-OHdG), inflammatory mediators (e.g., IL-6 and TNF-α), and epigenetic signatures may serve not only as indicators of cancer risk but also as measurable endpoints for evaluating the effectiveness of polyphenol-based dietary interventions [95, 108]. Incorporating these biomarkers into prevention strategies supports the development of evidence-based functional-food interventions to modulate molecular pathways involved in tumor initiation and progression [101–105].

Several challenges must be addressed before dietary polyphenols can be effectively integrated into clinical practice for the prevention of hereditary cancer. These include limited bioavailability, interindividual variability in metabolism mediated by gut microbiota,

and the need for standardized formulations and dosages. In addition, most available evidence derives from preclinical models or small-scale human studies. Large, randomized controlled trials in genetically predisposed populations are therefore needed to validate both efficacy and safety.

In summary, dietary polyphenols represent a promising adjunct to biomarker-driven precision prevention in individuals with hereditary cancer syndromes. By targeting multiple oncogenic pathways and modulating the epigenome, polyphenols may delay or mitigate carcinogenesis in high-risk individuals. The integration of molecular biomarkers as both predictors and monitoring tools may further optimize this preventive approach, aligning with the broader goals of personalized oncology and functional food science.

Novelty of the research: This review presents an integrative perspective on hereditary cancer prevention by linking prognostic biomarker profiling, oxidative-stress mechanisms, and dietary polyphenol-based strategies within the framework of functional food science. Importantly, it contextualizes these strategies within the Functional Food Centre's 17-step functional food development framework, which emphasizes systematic validation of bioactive compounds, biomarker-guided evaluation of physiological effects, and responsible translation of scientific findings into functional food applications [30-32, 114-117]. By positioning polyphenols not only as bioactive molecules but also as potential functional food ingredients, this review highlights a structured pathway for developing evidence-based nutritional interventions to reduce hereditary cancer risk [101–105].

Unlike conventional discussions of hereditary cancer that focus primarily on germline mutations and surveillance, the present review highlights how oxidative-stress biomarkers, redox-sensitive signaling pathways, hemorheological alterations and selected dietary polyphenols may be integrated into a broader precision-prevention framework. By connecting hereditary cancer biology with contemporary concepts in functional food science, the review strengthens the rationale for developing evidence-based nutritional approaches that complement molecular risk stratification in individuals with a genetic predisposition.

CONCLUSION

Hereditary cancer syndromes pose a significant clinical challenge because of the early onset, high penetrance, and aggressive nature of tumors linked to germline mutations in DNA-repair and cell-cycle regulatory genes. In this context, prognostic biomarkers have become essential tools for individual risk assessment, surveillance planning, and early therapeutic intervention. Although the utility of traditional and emerging biomarkers is well recognized, their role in hereditary syndromes requires further refinement because of distinct tumor biology and variable marker expression profiles.

This review highlights the multifactorial pathogenesis of hereditary tumors, emphasizing the role of germline mutations in tumor-suppressor genes, which not only impair DNA-repair pathways but also alter redox homeostasis and metabolic reprogramming. In addition to promoting genomic instability, oxidative stress serves as both a cause and a consequence of tumorigenesis, fostering tumor-cell survival, immune evasion, and therapeutic resistance.

Despite considerable advances, several challenges remain. The prognostic significance of oxidative-stress markers in hereditary cancer syndromes is underexplored; validated prognostic biomarkers specific to hereditary cancers remain limited compared with those for sporadic cases; and current clinical risk models often fail to integrate dynamic redox markers or hemorheological profiles. These gaps underscore the need for multidimensional biomarker models that

incorporate genetic, biochemical, and biophysical data to enhance precision oncology for high-risk individuals.

Importantly, as precision oncology continues to evolve, integrating molecular insights with modifiable lifestyle interventions is increasingly recognized as a forward-looking strategy. Among these, dietary polyphenols have shown significant promise as adjunctive agents in the chemoprevention of hereditary cancers. Through their antioxidants, anti-inflammatory, and epigenetic effects, polyphenols such as resveratrol, curcumin, EGCG, and quercetin can modulate signaling pathways disrupted by hereditary mutations, enhance genome stability, suppress tumor-promoting inflammation, and restore tumor-suppressor gene expression.

From the perspective of functional food science, translating polyphenol research into preventive strategies requires systematic validation of bioactive compounds, health claims, and biomarker responses. The Functional Food Centre's 17-step functional food development framework provides a structured pathway for this process, encompassing identification of bioactive compounds, mechanistic research, biomarker validation, clinical evaluation, and responsible translation into dietary recommendations [30-32]. Applying this framework to polyphenol-based interventions may accelerate the development of functional foods specifically designed to modulate oxidative stress and redox-dependent pathways associated with hereditary cancer risk.

The use of biomarkers not only for prognostication but also as dynamic indicators of dietary intervention efficacy represents a novel frontier in personalized prevention within the framework of functional food science. Measurement of oxidative-stress markers, pro-inflammatory cytokines, and epigenetic modifications may enable real-time adjustment of dietary strategies to optimize preventive outcomes in high-risk individuals.

In conclusion, the convergence of biomarker-driven surveillance and nutritional chemoprevention offers a compelling, multidimensional approach to managing hereditary cancer risk. Future research should focus on validating the preventive efficacy of polyphenols in large, genetically stratified cohorts and on establishing biomarker-based protocols that integrate lifestyle interventions into personalized clinical care pathways. Future studies should also evaluate whether polyphenol-rich functional foods, standardized for bioactive composition and supported by biomarker-based monitoring, can serve as practical adjuncts in personalized prevention strategies for individuals with hereditary cancer susceptibility. Such an approach holds promise not only for delaying cancer onset in genetically predisposed populations but also for improving long-term outcomes through noninvasive, sustainable prevention.

List of Abbreviations: 8-hydroxy-2'-deoxyguanosine, 8-OHdG; CAT, catalase; ECGC, epigallocatechin gallate; EMT, epithelial–mesenchymal transition; FFC, Functional Food Centre; GPX, glutathione peroxidase; GSTs, epithelial–mesenchymal transition; HBOC, Hereditary Breast and Ovarian Cancer; HIF-1α, hypoxia-inducible factor-1α; HR, homologous recombination; KEAP1, Kelch-like ECH-associated protein 1; MDA, malondialdehyde; MMR, mismatch-repair; mtDNA, mitochondrial DNA; NET, neutrophil extracellular traps; NRF2, nuclear factor erythroid 2–related factor 2; NF-κB, nuclear factor-κB; PARP, poly polymerase; ROS, reactive oxygen species; SCFA, short-chain fatty acid; SOD, superoxide dismutase; TILs, tumor-infiltrating lymphocytes; TMB, tumor mutational burden; VEGF, vascular endothelial growth factor.

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