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Antioxidants as a Double-Edged Sword: Protective and Paradoxical Roles in Obesity-Associated Carcinogenesis

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ABSTRACT

Antioxidants are central to cellular defense against oxidative stress, a critical driver of obesity-associated carcinogenesis. Excess adiposity generates chronic inflammation, insulin resistance, and elevated production of reactive oxygen species, which contribute to DNA damage and tumorigenesis. Antioxidants from dietary and endogenous sources are thought to counteract these effects, offering potential protection against cancer. However, emerging evidence suggests paradoxical roles: under certain conditions, antioxidants may promote tumor progression by enabling cancer cell survival, interfering with apoptosis, or altering redox-sensitive signaling pathways. This duality complicates the therapeutic promise of antioxidants in obesity-driven cancer risk. This review explores the mechanistic basis of antioxidant action in obesity-related carcinogenesis, highlighting protective effects and paradoxical outcomes. It examines evidence from preclinical and clinical studies, discusses the role of dietary, pharmacological, and endogenous antioxidants, and outlines implications for prevention and therapy. Ultimately, antioxidants should be viewed as a double-edged sword, with context-dependent effects that warrant careful evaluation in obesity-associated cancer management.

Keywords: antioxidants, obesity, cancer, oxidative stress, redox signaling

INTRODUCTION

Obesity is a rapidly growing global health problem, strongly associated with increased incidence and mortality from cancers of the breast, colon, endometrium, pancreas, and other organs [1]. One of the main mechanistic links between obesity and cancer is oxidative stress, which results from an imbalance between the generation of reactive oxygen species and the ability of antioxidant defenses to neutralize them [2]. Excess adiposity promotes oxidative stress through mitochondrial dysfunction, chronic low-grade inflammation, and metabolic dysregulation [3]. Antioxidants have therefore been proposed as promising modulators of obesity-associated carcinogenesis. By neutralizing reactive oxygen and nitrogen species, antioxidants protect DNA, proteins, and lipids from oxidative damage [4]. They also regulate redox-sensitive signaling pathways implicated in cell proliferation, apoptosis, and immune responses. However, growing evidence indicates that antioxidants may have paradoxical effects, sometimes enhancing cancer progression rather than preventing it. For example, exogenous antioxidant supplementation in certain contexts can promote tumor survival by attenuating oxidative stress that would otherwise induce cancer cell death [5]. This duality underscores the need for a nuanced understanding of antioxidant action. This review examines the interplay between antioxidants, obesity, and cancer, focusing on their protective roles and paradoxical pro-tumorigenic effects.

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Oxidative Stress in Obesity-Associated Carcinogenesis

Sources of Oxidative Stress in Obesity

Adipose tissue expansion in obesity is associated with increased production of reactive oxygen species [6]. Mitochondrial overload, activation of NADPH oxidases, and inflammatory cytokine signaling all contribute to enhanced oxidative stress [7]. Adipocytes and infiltrating macrophages secrete tumor necrosis factor alpha and interleukin-6, which further stimulate oxidative pathways [8]. These processes lead to DNA damage, lipid peroxidation, and protein modification, creating a fertile ground for carcinogenesis.

Oxidative Stress as a Driver of Cancer

Reactive oxygen species act as mutagenic agents and as second messengers in oncogenic signaling [9]. They induce DNA strand breaks and base modifications, which can result in mutations if not repaired. At the signaling level, oxidative stress activates transcription factors such as NF-κB, HIF-1α, and STAT3, promoting cell proliferation, angiogenesis, and survival [10]. In obesity, persistent oxidative stress combines with insulin resistance and chronic inflammation, accelerating tumor initiation and progression [11].

Protective Roles of Antioxidants

Endogenous Antioxidant Defenses

Cells maintain a complex network of enzymatic antioxidants, including superoxide dismutase, catalase, and glutathione peroxidase, which detoxify reactive oxygen species [12]. Non-enzymatic systems such as glutathione and thioredoxin provide additional buffering. In obesity, these systems are often impaired, and boosting their function has been shown in experimental models to reduce tumorigenesis [13].

Dietary Antioxidants

Natural antioxidants found in fruits, vegetables, and whole grains have been linked to a lower risk of cancer. Vitamin C scavenges free radicals and supports immune defenses, while vitamin E protects cell membranes from lipid peroxidation [14]. Polyphenols such as resveratrol, curcumin, and catechins exhibit both antioxidant and anti-inflammatory properties, modulating redox signaling pathways relevant to cancer prevention [15]. Epidemiological studies often show inverse associations between diets rich in antioxidants and cancer incidence, though supplementation trials have yielded mixed results [16].

Mechanistic Evidence of Protection

Antioxidants protect against obesity-associated carcinogenesis through multiple mechanisms. They reduce DNA damage, inhibit pro-inflammatory cytokine production, and modulate signaling pathways such as PI3K/Akt and MAPK [17]. In preclinical studies, antioxidant-rich diets have attenuated tumor growth in obese models by restoring redox balance and reducing systemic inflammation [18].

Paradoxical Roles of Antioxidants

Antioxidants and Cancer Cell Survival

Although antioxidants protect normal cells from oxidative damage, they can paradoxically promote survival of malignant cells [19]. Cancer cells often exist in a state of elevated oxidative stress, which can limit proliferation or trigger apoptosis [20]. Many conventional therapies, including chemotherapy and radiotherapy, exploit this vulnerability by further increasing reactive oxygen species beyond tolerable thresholds. Exogenous antioxidants may counteract this effect, shielding cancer cells from oxidative damage, enabling continued proliferation, and reducing therapeutic efficacy [21]. In obesity, where chronic oxidative stress is prevalent, antioxidant supplementation can inadvertently support the survival of pre-malignant or malignant cells by dampening ROS-mediated growth suppression [22].

Pro-oxidant Activity at High Doses

Under certain conditions, antioxidants can switch roles and act as pro-oxidants, generating reactive oxygen species rather than neutralizing them. For instance, high doses of vitamin C can produce hydrogen peroxide in the presence of transition metals, leading to oxidative damage of DNA and proteins [23]. Similarly, β-carotene supplementation in smokers was associated with increased lung cancer incidence, likely due to pro-oxidant effects in tissues with pre-existing inflammation [24]. These observations indicate that antioxidant activity is dose- and context-dependent, with potential for harm when administered at supra-physiological levels or in high-risk populations [25].

Modulation of Redox-Sensitive Signaling

Antioxidants can also interfere with redox-sensitive signaling pathways critical for tumor suppression. By reducing oxidative stress, they may suppress activation of p53 and other apoptotic pathways, allowing damaged cells to evade programmed cell death [26]. This paradox is particularly important in obesity, where elevated ROS initially trigger

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cell-cycle checkpoints and DNA repair but also drive mutagenesis [27]. Excessive antioxidant activity may shift this balance toward cell survival, enhancing tumor progression.

Evidence from Clinical Studies

Clinical trials reinforce the complexity of antioxidant effects. The ATBC study reported increased lung cancer incidence in male smokers receiving β-carotene, while other trials with vitamin E or selenium showed no reduction in cancer incidence [28]. These findings highlight that antioxidant supplementation, particularly at high doses or in high-risk individuals, may have unintended and sometimes harmful consequences. Careful evaluation of dose, timing, and patient context is therefore critical.

Contextual Determinants of Antioxidant Effects

Dose and Source

The effectiveness of antioxidants in modulating obesity-associated carcinogenesis is highly dependent on dose and source [29]. While moderate intake of antioxidants through whole foods is generally beneficial, excessive supplementation can produce unintended consequences. Whole foods such as fruits, vegetables, nuts, and teas provide a complex mixture of antioxidants, including vitamins, polyphenols, flavonoids, and carotenoids [30]. These compounds often act synergistically, enhancing free radical scavenging, modulating redox-sensitive signaling pathways, and supporting immune function. In contrast, high-dose isolated supplements may lack this synergistic interaction and, in certain contexts, act as pro-oxidants, especially when administered at supra-physiological levels [31]. This distinction underscores the importance of favoring natural dietary sources over indiscriminate supplementation for long-term health benefits.

Timing of Intervention

Timing is another critical determinant of antioxidant effects. Early in obesity-related carcinogenesis, antioxidants can mitigate DNA damage, reduce chronic inflammation, and improve metabolic function, thereby preventing tumor initiation [32]. However, in established tumors, excessive antioxidant activity may paradoxically promote cancer cell survival by attenuating oxidative stress that would otherwise induce apoptosis or senescence [33]. For instance, cancer cells in a high oxidative environment may rely on ROS-mediated signaling to maintain a balance between proliferation and death; exogenous antioxidants can disrupt this balance, enhancing tumor growth and resistance to therapy [34]. Therefore, interventions must be carefully timed, with emphasis on preventive or early-stage strategies rather than indiscriminate use in advanced cancer.

Genetic and Metabolic Context

Individual variability also significantly influences the impact of antioxidants. Genetic polymorphisms in enzymes regulating redox metabolism, such as superoxide dismutase, catalase, and glutathione peroxidase, can alter the efficiency of ROS detoxification and modulate responses to antioxidant supplementation [35]. Additionally, metabolic health, including the degree of obesity, insulin resistance, lipid dysregulation, and exposure to environmental pollutants, shapes oxidative stress levels and determines whether antioxidants exert protective or paradoxical effects. Personalized assessments of redox status, genetic background, and metabolic profile may therefore guide optimal antioxidant interventions [36].

Implications for Therapy and Prevention

From a therapeutic and preventive perspective, emphasis should remain on antioxidant-rich diets rather than high-dose supplements. Integrative approaches combining diet, weight management, physical activity, and targeted antioxidant therapies hold the greatest potential for reducing obesity-associated cancer risk. Pharmacological agents such as metformin and N-acetylcysteine may provide additional modulation of oxidative stress, though clinical translation requires careful consideration of context, timing, and individual susceptibility [37]. Public health strategies should focus on dietary patterns, obesity prevention, and education about the nuanced role of antioxidants. Future research integrating systems biology, exposomics, and biomarker-driven interventions is needed to define personalized strategies that maximize protective benefits while minimizing potential risks.

CONCLUSION

Antioxidants occupy a paradoxical position in obesity-associated carcinogenesis. On one hand, they counteract oxidative stress, reduce DNA damage, and attenuate inflammation, offering protective effects against cancer initiation. On the other hand, they may inadvertently promote tumor survival and interfere with therapeutic efficacy under certain conditions. The balance between protective and paradoxical roles depends on dose, source, timing, and individual context. Moving forward, strategies should emphasize whole-food dietary antioxidants, integrative approaches to weight management, and personalized interventions informed by redox biology. Recognizing antioxidants as a double-edged sword provides a more realistic framework for their role in obesity-related cancer prevention and therapy.

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