THE INFLUENCE OF VITAMIN D ON THE PREVENTION AND TREATMENT OF MALIGNANT DISEASES

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review paper

Summary

Vitamin D has long been recognized for its essential role in maintaining healthy bones and teeth. In recent years, there has been increasing research into the potential influence of vitamin D on malignant diseases. It is estimated that more than 10 million people die from cancer each year, making it one of the leading causes of death globally. While many factors contribute to cancer development, including genetic and environmental factors, research has suggested that vitamin D may play a role in reducing the risk of certain types of cancer. Vitamin D has numerous physiological functions, such as anti-inflammatory, immunomodulatory, proapoptotic, and antiangiogenic effects. Preclinical studies have shown that it could inhibit carcinogenesis, slowing tumor progression by stimulating cell differentiation and inhibiting cancer cell proliferation. Several types of cancer have been studied concerning vitamin D. While more research is needed, some evidence suggests that vitamin D may play a role in reducing the risk of certain types of cancer. Maintaining adequate vitamin D levels through sunlight exposure, diet, or supplementation may be essential in promoting overall health and reducing the risk of malignant diseases.

Keywords: cancer prevention, malignant diseases, vitamin D

Introduction

Malignant diseases are the leading cause of mortality in the world. They are responsible for 10 million deaths in 2020 and cause every sixth death. The most common cancer sites are breast, lung, colon, and prostate. Risk factors for most malignancies include smoking, high body mass index, alcohol consumption, reduced fruit and vegetable intake, and lack of physical activity (Global Cancer Observatory, 2022). One out of three people in Croatia will be diagnosed with cancer during their lifetime. Fortunately, progress in diagnosing and treating malignant diseases has led to a decrease in mortality and an increasing number of people who survive many years after diagnosis. In most developed European countries, the death rate from cancer decreases yearly. In Croatia, mortality from cancer reduces by 2% on average every year (Croatian Institute for Public Health, 2023). In the prevention and treatment of cancer, there are currently no clear guidelines on the additional compensation of specific vitamins and minerals (Harvie, 2014).

Vitamin D

Sources of Vitamin

Ergocalciferol and cholecalciferol are two different forms of vitamin D, and they differ in their natural sources and production pathways. Ergocalciferol (Vitamin D2) is derived from plant sources; certain fungi, including yeast and mushrooms, synthesize it when exposed to ultraviolet (UV) light. Plants, such as some types of algae, can also produce ergosterol, which can be converted into ergocalciferol through a similar UV light-mediated process. Cholecalciferol (Vitamin D3) is primarily derived from animal sources, such as fatty fish (e.g., salmon, mackerel) and fish liver oils (Benedik, 2022) (Table 1). It is synthesized in the skin of animals, including humans, when 7-dehydrocholesterol, a compound present in the skin, is exposed to UV-B radiation from sunlight. Regarding supplementation, both ergocalciferol (D2) and cholecalciferol (D3) are used to address vitamin D deficiency. However, cholecalciferol (D3) is the most commonly used form for supplementation due to its greater effectiveness in raising and maintaining vitamin D levels in the body. Cholecalciferol is also considered the more bioavailable and potent form of vitamin D. It closely resembles the natural form of vitamin D produced in the skin, making it more readily utilized by the body. Ergocalciferol (D2) is still used in some cases, such as for vegans who prefer a plant-based source or for patients with specific medical conditions (Dominguez et al., 2021; Cashman et al., 2014).

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Table 1. Foods rich in vitamin D

Food	Amount	Vitamin D (IU)
Egg yolk	1	42
Salmon	100 g	360
Swoldfish	300 g	566
Sardine	50 g	250
Milk	1 cup	98
Cod liver oil	1 soup spoon	1360
Tuna	300 g	154

Vitamin D metabolism

Vitamin D obtained from food, supplements, or sun exposure is biologically inactive and must undergo two hydroxylations to be activated. In the blood, it is transported by vitamin D-binding protein (VDBP) to the liver, where it is hydroxylated to produce 25-hydroxyvitamin D3 (25(OH)D3), i.e., calcidiol, the primary circulating form of vitamin D with a half-life of about 2-3 weeks. The final step of hydroxylation occurs in the renal proximal convoluted tubules, where CYP27B1 metabolizes 25 (OH)D3 into calcitriol, 25(OH)2D3, the functional and hormonally active form of vitamin D. The half-life of calcitriol is about 6 - 8 hours, which is why it is not a good indicator of vitamin D status in the body. To determine the concentration of vitamin D, the calcidiol level is monitored. In the kidney, CYP27B1 is regulated by parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and calcitriol itself. 25(OH)D3 can also be converted to 24.25(OH)2D3 by CYP24A1, limiting the amount of calcitriol when its circulating level is high (Christakos et al., 2015; Peixoto et al., 2022).

VDBP is a multifunctional protein primarily known for transporting vitamin D and its metabolites in the bloodstream. However, emerging research suggests that VDBP may have additional biological functions, including anti-inflammatory and immunomodulatory effects, independent of its role as a vitamin D transporter. VDBP inhibits the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), in various cell types. VDBP has also been suggested to influence the maturation and function of immune cells, including dendritic cells, macrophages, and T cells. It also exhibits antimicrobial properties by binding to microorganisms, such as bacteria and viruses, and enhancing their clearance by immune cells. It can facilitate the opsonization and phagocytosis of pathogens, contributing to the innate immune response (Chun et al., 2010).

The recommended intake of vitamin D

Vitamin D promotes calcium absorption in the intestines, enables normal bone mineralization by maintaining the concentration of calcium and phosphate in the serum, is needed for bone remodeling, and promotes the reduction of inflammation. Vitamin D is important in preventing the onset and alleviating the clinical picture of multiple sclerosis, rheumatoid arthritis and inflammatory bowel diseases. Vitamin D deficiency is also associated with schizophrenia, depression and lung diseases. Recommended values of 25(OH)D are 30-50 ng/mL (75-125 nmol/L). Mild insufficiency refers to a relatively low vitamin D level but still within a suboptimal range. This stage may be characterized by serum 25-hydroxyvitamin D levels between 20 and 30 ng/mL (50-75 nmol/L). There may not be significant clinical symptoms or complications at this stage, but it indicates that vitamin D levels are not at an ideal class for optimal health. Moderate insufficiency indicates a further decline in vitamin D levels. This stage may be defined by serum 25-hydroxyvitamin D levels between 10 and 20 ng/mL (30-50 nmol/L). Severe insufficiency or deficiency represents significantly low vitamin D levels. This stage may be characterized by serum 25-hydroxyvitamin D levels below 10 ng/mL (30 nmol/L) (Vranešić et al., 2016; Holick et al., 2011). Observational studies have shown that over 40% of Europeans have vitamin D deficiency (Amrein et al., 2020). In the elderly, the numbers are much more dramatic, and some studies have shown that only 15% of older adults have optimal vitamin D status (Kweder et al., 2018). Inadequate vitamin D status is associated with muscle weakness, functional impairment, depression, and increased risk of falls and fractures. Hazards for the appearance of a deficit include a dark complexion, too little sun exposure, older age, obesity, and certain types of pharmacotherapy (antiepileptics, metformin, bisphosphonates, cytostatics, thiazolidinediones, diuretics, calcium channel blockers, ACE inhibitors) (Gröber et al., 2012). The

recommended dietary vitamin D intake for adults over 18 is 600 IU, increasing to 800 IU after age 71. However, to raise serum 25(OH)D levels continuously above 30 ng/mL (75 nmol/L), it is recommended to take at least 1500 – 2000 IU/day of vitamin D. In adults with known vitamin D deficiency, treatment with 50 000 IU of vitamin D2 or vitamin D3 once weekly for eight weeks or 6000 IU of vitamin D2 or D3 daily to achieve a serum 25(OH)D level above 30 ng/mL, followed by maintenance of 1500–2000 IU /day is recommended. In obese patients, patients with malabsorption syndrome, and patients taking medications that affect vitamin D metabolism, a two to three times higher dose (at least 6000-10 000 IU/day) of vitamin D is recommended to treat vitamin D deficiency until reaching a level of 25(OH)D above 30 ng/mL, and after that maintenance of 3000–6000 IU/day (Holick et al., 2011). Vitamin D supplementation has both calcemic and non-calcemic effects. Low-dose supplementation maintains calcium levels and supports bone health, while high-dose supplementation can increase serum calcium levels, potentially affecting organs. In addition, adequate vitamin D levels may reduce the risk of autoimmune diseases and respiratory infections, improve muscle strength and reduce fall risk, positively impact mood and mental well-being, and play a role in preventing and managing conditions like cardiovascular disease, diabetes, and certain cancers (Holick et al.,2011; Ross et al., 2011).

Liver diseases can contribute to vitamin D deficiency through multiple mechanisms. The liver plays a crucial role in the synthesis and activation of vitamin D. In liver diseases such as cirrhosis, impaired liver function can lead to reduced production of 25-hydroxyvitamin D, the primary circulating form of vitamin D. This can result in lower overall vitamin D levels in the body. Furthermore, liver diseases can disrupt the metabolism of vitamin D and its binding proteins, affecting its availability and utilization. As a result, individuals with liver diseases are at an increased risk of developing vitamin D deficiency (Kitson et al., 2012; Arteh et al., 2010). Also, certain gastroenterological diseases can interfere with the absorption and metabolism of vitamin D, leading to reduced biological availability. Conditions such as Crohn's, celiac, and inflammatory bowel disease (IBD) can impair the absorption of fat-soluble vitamins, including vitamin D, due to intestinal inflammation, malabsorption, or surgical interventions. Additionally, conditions affecting the bile acid metabolism or the bile ducts, such as primary biliary cholangitis, can disrupt the enterohepatic circulation of vitamin D and impair its absorption and utilization. Consequently, individuals with these gastroenterological conditions may experience reduced levels of biologically active vitamin D (Ardizzone et al., 2011; Lin et al., 2016). Kidney diseases can lead to vitamin D deficiency due to impaired renal function and decreased synthesis of active vitamin D metabolites. The kidneys are crucial in converting inactive vitamin D (calcidiol) into its active form (calcitriol). In conditions such as chronic kidney disease (CKD) or end-stage renal disease (ESRD), there is a decline in renal function, resulting in reduced production of calcitriol. This can lead to inadequate activation of vitamin D and subsequent deficiency. Moreover, kidney diseases can cause urinary losses of vitamin D-binding protein, further contributing to lower vitamin D levels (Wolf et al, 2007; Isakova et al, 2011).

Vitamin D and cancer

Observational studies have established an association between low vitamin D concentrations and an increased prevalence of diabetes, hypertension, hyperlipidemia, and peripheral vascular disease. Many studies indicate a connection between low vitamin D concentrations and certain cancers (Wang et al., 2017). It has been shown that patients with a higher level of circulating vitamin D in the blood have a significantly lower risk of death, especially in the case of colorectal cancer. Such optimistic results support the concept of targeted intervention with vitamin D (Jeon et al., 2018). Vitamin D has numerous physiological functions, such as anti-inflammatory, immunomodulatory, proapoptotic, and antiangiogenic effects. Preclinical studies have shown that it could inhibit carcinogenesis, slowing tumor progression by stimulating cell differentiation and inhibiting cancer cell proliferation. Vitamin D can therefore inhibit tumor invasiveness and its propensity to metastasize, potentially reducing cancer mortality (Bouillon et al., 2006; Bouillon et al., 2008).

Colorectal cancer

According to the World Health Organization, colorectal cancer is the most frequently diagnosed cancer in men and the second in order in women (Global Cancer Observatory, 2022). Although the incidence of colorectal cancer has decreased in the total population over the last decades, it has increased in the population under 50. Many studies have shown how diet and lifestyle have a significant influence on the development of the disease. A diet rich in red meat and poor in fiber, fruits, and vegetables increases the risk of colorectal cancer, as does insufficient physical activity. The impact of low calcium intake and vitamin

D hypovitaminosis on the risk of disease and worse clinical outcomes in patients with colorectal cancer is also known (Thanikachalam et al., 2019). Several meta-analyses have reported an association between lower vitamin D levels and increased colorectal cancer risk. In a study that collected data from 17 cohorts, including 5706 patients with colorectal cancer and 7107 controls, it was demonstrated that higher levels of circulating vitamin D lead to a statistically significant reduction in the risk of colorectal cancer in women and a non-statistically significant reduction in men (McCullough et al., 2017).

The biological action of calcitriol is mediated by the vitamin D receptor (VDR), which is a member of the steroid hormone receptor family. VDR was first identified in the small intestine and was later found in almost all tissues, while the intestine is the organ with the highest expression of VDR. Altered expression of VDR and other essential proteins in the synthesis and catabolism of vitamin D has been observed in many different tumors. CYP27B1 and VDR are strongly expressed during the early progression of colorectal cancer in well-differentiated tumors. They are downregulated in poorly differentiated tumors, while CYP24A1 is upregulated, suggesting an autocrine/paracrine growth control by active metabolites of vitamin D in colorectal tissue as a restriction against tumor progression (Christakos et al., 2015; Peixoto et al., 2022). VDR expression increases in hyperplastic polyps and the early stages of tumorigenesis but decreases in the late stages of poorly differentiated tumors and is absent in associated metastases. Colorectal cancer with higher expression of VDR responds better to the addition of calcitriol, but regulation of VDR in tumor cells by some transcription factors reduces its anticancer effect (Matusiak et al., 2005; Christakos et al., 2015).

Vitamin D has been shown to play a significant role in preventing colon cancer by regulating the homeostasis of the intestinal epithelium through multiple mechanisms. It exerts its effects by modulating the oncogenic Wnt signaling pathway and inhibiting tumor-promoting inflammation. Vitamin D acts as a negative regulator of the Wnt signaling pathway, which plays a crucial role in the development and progression of colon cancer. The Wnt pathway regulates the growth and differentiation of intestinal epithelial cells: and interacts with Wnt signaling components, such as β-catenin and the Wnt co-receptor LRP5/6, to suppress aberrant activation of the pathway. This modulation helps maintain the balance between cell proliferation and differentiation, preventing the uncontrolled growth of colon cancer cells (Palmer et al, 2011; Larriba el al., 2014).

Vitamin D also possesses anti-inflammatory properties that help inhibit tumor-promoting inflammation in the colon. Chronic inflammation is a risk factor for colon cancer development and progression. Vitamin D exerts its anti-inflammatory effects by modulating the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while promoting the production of anti-inflammatory cytokines. This modulation helps create an environment that discourages tumor growth and progression. (Byers et al., 2012; Bharti et al., 2002). Growing evidence shows that vitamin D is crucial in regulating the gut microbiota and promoting a healthy gut environment. Dysbiosis, or an imbalance in gut microbiota, has been linked to colorectal cancer (CRC) development and progression. Vitamin D has been shown to exert indirect antitumor effects in CRC by modulating the gut microbiota. Studies have demonstrated that vitamin D deficiency is associated with changes in the composition and function of the gut microbiota, with a reduction in beneficial bacteria such as Bifidobacterium and Lactobacillus and an increase in potentially harmful bacteria such as Fusobacterium and Enterobacteriaceae. In addition, vitamin D supplementation has been shown to improve gut microbial diversity and promote the growth of beneficial bacteria in animal models of CRC (Song et al., 2020; Sukik et al., 2023).

One study examined the association between pre-diagnosis plasma 25-hydroxyvitamin D levels and survival outcomes in patients with stage I-IV CRC. Higher vitamin D levels were associated with improved overall survival and disease-free survival in patients with stage III CRC, but no significant association was observed in patients with other stages (Ng et al., 2008). Other study investigated the association between preoperative serum vitamin D levels and survival outcomes in patients with CRC. Higher vitamin D levels were associated with improved overall survival and disease-free survival, particularly in patients with stage III CRC (Mezawa et al., 2010).

Breast cancer

Breast cancer is the most common cancer in women. Every year, 2 million women worldwide fall ill with this disease. Numerous risk factors for breast cancer have been identified, including race, ethnicity, family history of cancer, genetic traits, and modifiable exposures such as increased alcohol consumption, physical inactivity, and exogenous hormones. Parity, older age at first pregnancy may influence breast cancer risk through long-term effects on sex hormone

levels or other biological mechanisms (Coughlin et al., 2019). Many studies have examined the association between vitamin D concentration and breast cancer risk, but the results are inconsistent. One meta-analysis showed that women with the highest quantile of circulating 25(OH)D had a 45% reduced risk of breast cancer compared to women with the lowest quantile (Chen et al., 2010). Another meta-analysis showed a gradual inverse association above the threshold of 27 ng/mL, but with flattening of the effects above 35 ng/mL in postmenopausal women but not in premenopausal women (Bauer et al., 2013). A randomized trial of over 25 000 men and women found no significant effect of vitamin D (2000 IU) with or without omega-3 supplementation on breast cancer incidence (Manson et al., 2020).

In breast cancer tissue, VDR expression has been reported to be inversely correlated with breast cancer aggressiveness. In benign breast lesions, VDR is significantly more pronounced than in breast cancer lesions (in situ and invasive). Also, VDR expression is higher in luminal A BC than in triple-negative breast cancer, which is the most aggressive type. Higher overall VDR expression in breast cancer is associated with tumor characteristics such as lower grade, smaller size, ER/PR positivity, lower Ki67 expression, and lower mortality risk. Previous studies have shown that VDR expression in breast cancer tissue decreased during tumor progression. Further research is needed on whether VDR expression can be a potential biomarker for breast cancer progression. (Vanhevel et al., 2022; Lopes et al., 2012).

Prostate cancer

About 1 in 8 men will be diagnosed with prostate cancer during their lifetime. About 6 out of 10 cases are diagnosed in men who are 65 or older, and it is rare in men under 40. Risk factors include age, family history, insulin-like growth factor, sexually transmitted diseases, obesity, smoking, alcohol consumption, vasectomy, and diet (Perdana et al., 2016). Studies investigating the association between 25(OH)D levels and cancer still did not answer the requested questions. A meta-analysis showed that men with elevated serum 25(OH)D levels have a higher risk of developing prostate cancer than men with lower serum 25(OH)D levels (Xu et al., 2014). One study found that the relationship varied by aggressiveness; higher levels of 25(OH)D increase the risk of low-grade prostate cancer (Gleason score 2-6) but reduce the risk of high-grade disease (Gleason score 8-10) (Schenk et al., 2014). A study involving 7808 participants showed that higher vitamin D levels could reduce the risk of death in prostate cancer patients,

concluding that vitamin D is an essential protective factor in the progression and prognosis of prostate cancer (Song et al., 2018).

Bladder cancer

Bladder cancer occurs three times more often in men than women, and the frequency increases with age. The most significant risk factor is smoking, which increases the risk of cancer by a minimum of 3 times. Over 50% of people with bladder cancer are smokers. Several studies have investigated the association between 25 (OH)D3 and bladder cancer. One study examined the effect of vitamin D supplementation on the effectiveness of cisplatin therapy used to treat bladder cancer. The results showed that low serum 25(OH)D3 levels were significantly associated with a worse response to cisplatin. Pretreatment of 25(OH)D3-deficient mice reduced tumor volume compared to cisplatin monotherapy (Bunch et al., 2019). The results of another study showed that a concentration of 25(OH)D3 ≥74 nmol/L is associated with a 60% lower risk of bladder cancer (Zhao et al., 2016). One study revealed that lower levels of vitamin D were associated with an increased risk of bladder cancer. Furthermore, the study examined the role of VDBP, a protein involved in vitamin D transport, and its association with bladder cancer risk. Interestingly, the findings suggested that higher VDBP levels were associated with a decreased risk of bladder cancer. This indicates that VDBP may play a significant role in the vitamin D pathway and its potential impact on bladder cancer development. These findings emphasize the importance of considering both vitamin D and VDBP levels in assessing the risk of bladder cancer. Further research is warranted to elucidate the underlying mechanisms by which vitamin D and VDBP exert their effects and to explore potential preventive strategies and therapeutic interventions targeting this pathway (Hektoen et al., 2021)

Lung cancer

Lung cancer is the most common cause of death from cancer. Smoking is known as the most critical risk factor, but there is still not much evidence about dietary supplements that would serve as lung cancer prevention. So far, several studies have been conducted that have examined the connection between vitamin D and lung cancer. One meta-analysis showed a significant reduction in lung cancer risk by 5% for every ten nmol/L increase in 25(OH)D3 concentration (Chen et al., 2015). Another study showed that vitamin D supplementation could improve survival in patients with early-stage lung adenocarcinoma (Akiba et al.,

2018). Another meta-analysis showed that the combination of vitamin D and calcium supplementation significantly reduced the incidence of lung cancer. Further studies are needed to examine whether a higher concentration of 25(OH)D in the serum could have a preventive role in lung cancer (Sun et al., 2021). Several studies have shown that vitamin D plays a crucial role in preventing lung cancer tumor growth, migration, and proliferation. One of the mechanisms through which vitamin D exerts its anticancer effects is by downregulating Histidine-rich calcium-binding protein (HRC). HRC is a protein involved in calcium homeostasis and is overexpressed in several types of cancer, including lung cancer. In one study, it was demonstrated that vitamin D treatment significantly inhibited lung cancer cell growth, migration, and proliferation in vitro and in vivo. The authors showed that vitamin D downregulated HRC expression in lung cancer cells, leading to a decrease in intracellular calcium concentration and subsequently inhibiting cancer cell growth (Liu et al., 2020).

Ovarian cancer

Ovarian cancer is called the "silent killer" because it is usually diagnosed late when the chances of a cure are already meager. Most cancers are diagnosed in stage III (51%) or IV (29%), where the five-year survival rate is only 42% and 26%, respectively. The risk is higher in women who have not given birth, who have given birth late, and those with later menopause. Pregnancy and oral contraceptives reduce the risk of cancer. The connection with environmental factors has not been proven with certainty (Piatek et al., 2022; Roett et al., 2009). A meta-analysis with almost a million participants concluded that vitamin D intake could not reduce the risk of ovarian cancer (Xu et al., 2021). On the other hand, a study conducted in Australia concluded that exposure to ambient ultraviolet radiation could reduce the risk of epithelial ovarian cancer (Tran et al., 2012). In another cohort study from Australia, higher serum 25(OH)D levels at diagnosis were shown to correlate significantly with more prolonged survival in women diagnosed with invasive ovarian cancer (Webb et al., 2015).

Pancreatic cancer

Pancreatic cancer is an insidious disease because, at the time of diagnosis, in 85% of cases, it has already spread to local structures or has metastasized to the liver and lungs. Risk factors include smoking, obesity, a positive personal or family history of diabetes or chronic pancreatitis, and various genetic syndromes

(e.g., MEN1, Lynch, VHL) (Klein et al.,2021). One study showed that people with the highest concentrations of 25 (OH)D have twice the risk of pancreatic cancer (Stolzenberg-Solomon et al.,2010). On the other hand, another study showed that higher levels of 25(OH)D were associated with a lower risk of pancreatic cancer (Wolpin et al., 2012). One meta-analysis studied the impact of vitamin supplementation and the risk of pancreatic cancer. It showed that vitamin D reduces the risk of pancreatic cancer by 25% and vitamin B 12 by 27% (Liu et al., 2018). A meta-analysis of 1 206 011 participants concluded that circulating 25(OH)D concentration is not associated with pancreatic cancer risk (Liu et al., 2013). Given the inconsistency of these studies, further studies are needed to determine whether there is an association between 25(OH)D concentration with this cancer.

Conclusion

Cancer is a complex and heterogeneous disease with different risk factors and etiology depending on the specific location and underlying biology. Research has shown that vitamin D may protect against certain types of cancer, such as colorectal, bladder, and lung cancer, while potentially increasing the risk for others, including prostate and pancreatic cancer. However, the evidence regarding vitamin D supplementation for cancer prevention is still insufficient and inconsistent. High-dose vitamin D supplementation is not recommended for cancer prevention at this time. The risks of bone loss, osteoporosis, and fractures are well-known in patients with malignant disease. Therefore, assessing and addressing vitamin D deficiency in these patients is essential. Monitoring 25(OH)D levels and providing appropriate replacement therapy for vitamin D deficiency can be beneficial. Patients undergoing treatments that negatively affect bone health, such as ovarian suppression/ablation, aromatase inhibitors, and androgen deprivation therapy, are advised to follow a calcium-rich diet, moderate exercise, and take daily vitamin D supplementation of 1000-2000 IU. In addition to vitamin D supplementation, maintaining a healthy lifestyle and practicing cancer prevention strategies are crucial. This includes maintaining a healthy weight, avoiding tobacco and excessive alcohol consumption, and participating in regular cancer screenings.

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