New approaches to reduce the risk of Cancer: A mini literature review

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Abstract

Cancer is the first or second leading cause of death before the age of 70 years in over 100 countries and ranks third or fourth in over 20 countries with 19 million new cancer cases and over 9 million mortalities in the year 2020 alone. Due to the high cost of cancer treatment, inefficiency in the eradication of all cancer cells and inaccessible healthcare for a large population in developing countries, the education of policy makers and the public in general on cancer prevention or cancer risk reduction measures is of utmost importance. These include the re-use of medications such as aspirin, foods such as soy and soy protein, vigorous intermittent physical activity, healthy eating (nutrition and diet) and vaccination. We aim to highlight and reiterate the importance of different approaches that reduce the risk of cancer, which may be alien or unknown in our society. These include the inclusion of foods such as soy and soy protein in our diet, vigorous intermittent physical activity, healthy eating (nutrition and diet) in general, vaccination and investment in the research of already existing drugs with known toxicity profiles.

The fact that a large number of cancer patients in low- and middle-income countries cannot afford therapy, means there is a dire need for prevention measures to be exploited and integrated alongside conventional cancer therapy. Policy makers and the public in general should be educated on these measures to relieve the financial and emotional burden on patients and society as a whole.

Keywords: Cancer, Reduce risk of cancer, Financial burden, aspirin, nutrition and diet, Vaccines

Introduction

Cancer is the first or second leading cause of mortality before the age of 70 years in over 100 countries and ranks third or fourth in over 20 countries (WHO, 2019). Globally, approximately 19 million new cancer cases and over 9 million mortalities due to cancer occurred in the year 2020 (GLOBOCON, 2020), out of which female breast cancer, lung, colorectal, prostate and stomach cancers make up 11.7%, 11.4%, 10.0%, 7.3% and 5.6% of the new cases respectively. Lung, colorectal, liver, stomach and female breast cancers make up 18%, 9.4%, 8.3%, 7.7% and 6.9% of the overall cancer mortalities respectively (Sung *et al*., 2021).

The different approaches to the prophylaxis and treatment of cancer are mainly targeted at preventing or reversing the different hallmarks of cancer, which consist of "sustaining proliferative signalling", "evading growth suppressors", "inducing angiogenesis", "enabling replicative immortality", "activating invasion and metastasis", "resisting cell death", "cancer-related inflammation", and recently "unlocking phenotypic plasticity", "nonmutational epigenetic reprogramming", "polymorphic microbiomes" and "senescent cells" (Hanahan and Weinberg, 2011; Hanahan, 2022). Treatments may include surgery, chemotherapy and radiation therapy. Alternative treatments include targeted therapy, immunotherapy, laser and hormonal therapy. Chemotherapy, which is the most common form of treatment for most cancers is inefficient in the eradication of all cancer cells due to alterations in the physiologic conditions of the tumour microenvironment (Behranvand *et al*., 2022). The treatment of cancer is accompanied by both emotional and financial burden which affects not only the patient, but the families as well. In one of the tertiary health facilities situated in south West Nigeria, the mean total cost for treatment incurred by patients with cancer was over $5,000 (USD). This overall treatment consumes over 95% of their mean annual income, which more often than not is sourced from family members. This eventually results in a negative financial impact to the society/community as a whole (Mustapha *et al*., 2020).

Due to the high cost of cancer treatment, inefficiency in the eradication of all cancer cells and inaccessible healthcare for a large population in developing countries, the education of policy makers and the public in general on cancer prevention or cancer risk reduction measures is of utmost importance.

This literature review aims to highlight and reiterate the importance of different approaches that reduce the risk of cancer, which may be alien or unknown in our society. These include the inclusion of foods such as soy and soy protein in our diet, vigorous intermittent physical activity, healthy eating (nutrition and diet) in general, vaccination and investment in the research of already existing drugs with known toxicity profiles.

Re-purposed drugs

These are drugs with proven pharmacokinetics and safety/toxicity profiles. Re-purposed drugs may be used either to reduce recurrence and metastasis or as prophylaxis in patients with high risk of developing cancer (Rodrigues *et al*., 2022). They include aspirin, naproxen, metformin, mebendazole, albendazole, acyclovir, doxycycline, thalidomide, artesunate, to name a few.

Aspirin

Studies on aspirin, an ortho-isomer has revealed cytotoxic and immunomodulatory effects on colorectal cancer cell lines (Kadhum *et al*., 2022; Kilari *et al*., 2018). Subjects that are known to experience a rise in thromboxane biosynthesis after radical cancer therapy, are most likely to benefit from the use of aspirin (Joharatnam-Hogan *et al*., 2023). The findings in a study by Guo *et al*., 2021 supports the use of aspirin, if initiated at a younger age to reduce the risk of colorectal cancer (CRC). The regular aspirin that is used medically is the ortho-aspirin (O-ASP), while meta-aspirin (M-ASP) and para-aspirin (P-ASP) are its synthesized positional isomers. Ortho-thioaspirin (O-TASP), meta- (M-TASP) and para-thioaspirin (P-TASP) are also synthesised aspirin analogues (Bashir *et al*., 2019).

Numerous studies have shown the effects of aspirin and its analogues on colorectal cancer, which reiterates their use in chemoprevention (Bashir and Nicholl, 2018). Studies in a CAPP2 (Colorectal Adenoma/carcinoma Prevention Programme) and an updated meta-analysis, concluded that the regular use of aspirin is associated with a decreased risk in the development of colorectal and other digestive tract cancers, which includes those with a genetic disposition to CRC such as Lynch syndrome and patients with PIK3CA-mutated tumors (Bosetti *et al*., 2020; Burn *et al.*, 2020). The inhibitory mechanisms caused by aspirin on CRC has paved way to identifying predictive biomarkers for its CRC chemoprevention. However, this reduced risk/chemoprevention is linked with protracted aspirin use (Grancher *et al*., 2022), easily leading to gastrointestinal

bleeding and peptic ulcer, which have been found to be mostly age-dependent (Li *et al*., 2017). Although aspirin use was recommended by the United States Preventive Services Task Force (USPSTF) for primary prevention of CRC in all patients aged 50 to 59 with a 10 year risk of cardiovascular events greater than 10% in 2016, an update states that USPSTF no longer recommends aspirin for the primary prevention of CRC because the evidence is unclear whether it reduces the risk of CRC incidence or mortality (USPSTF, 2022). Aspirin or/and its analogues have been found to exhibit additive and synergistic effects when used in combination with other medications in CRC cell lines (Voutsadakis *et al*., 2010; Kilari *et al*., 2019; Susan *et al*., 2023).

Metformin

Metformin, a first line therapy for glucose control in Type 2 diabetic patients is a lipophilic biguanide which inhibits gluconeogenesis and improves glucose utilization (Mallik and Chowdhury, 2018). Studies show metformin to exhibit anti-tumourigenic effect by activating AMP-kinase, which inhibits vascular endothelial growth factor expression via mTORC1 (mammalian target of rapamycin) (Tadakawa *et al*., 2014). Other mechanisms include reduction of insulin-like growth factor-1, leptin and cancer stem cells. Clinical studies have been carried out for the effect of metformin in nondiabetic cancer patients. However, results are controversial. The difference in results could be resolved by further investigating the immunomodulatory effect of metformin on cancer cells (Chen *et al*., 2020).

Mebendazole

Mebendazole, an antihelmintic drug shows its effect on anticancer pathways in several studies. It increases cell cycle arrest in G2/M phase, Caspase-3 and apoptosis by decreasing Bcl-2 (Mohi-ud-din *et al*., 2023). Due to its ability to penetrate the blood-brain barrier, mebendazole has been effective for the treatment of malignant gliomas. It can also be used in combination with temozolomide (Bai *et al*., 2011). It also exhibited synergistic effects in suppressing tumour growth in prostate cancer with docetaxel (Rushworth *et al*., 2020). Although mebendazole has hadvarious promising outcomes in the treatment of malignant gliomas, there are a number of challenges such as physicochemical properties, poor bioavailability with significant individual pharmacokinetic variability that needs to be resolved for effective oncological use (Meco *et al.*, 2023).

Doxycycline

This is an antibiotic of the tetracycline family, used as therapy to different infections. It has been found to have antiproliferative effect on bone and prostate carcinomas, suppression of tumour progression and as such beneficial for patients with breast cancer who are at risk for developing osteolytic bone metastasis (Mohi-ud-din *et al*., 2023). Further *in vivo* and clinical trials are needed to evaluate and confirm the use of doxycycline as an antineoplastic agent.

Artesunate

Artesunate is from the plant extract, artemisinin, that have been found to be effective in the treatment of malaria. Data shows antiproliferative and pro-apoptotic effects on lyphoma, myeloma, hepatocellular and cervical cancer cells (Holien *et al*., 2013; Vandewynckel *et al*., 2014; Zhang *et al*., 2024), and thus chemopreventive effects (Verma *et al*., 2017). Studies have shown artesunate to also have antiangiogenic effects in renal cancer and hepatocellular carcinoma, resulting in a decrease in tumour development *in vivo* and a decrease in endothelial growth factor (Mohi-ud-din *et al*., 2023). However, outcomes of *in vitro* studies have been found to be related to the complexity of the tumour model used and such it is of utmost importance for artesunate to be evaluated before treatment of the individual patient to ensure its benefits and prevent side effects (Niederreiter et al., 2023). A review of case studies on glioma concluded artesunate to effective without harmful side effects, even if combined with alkylating agent (Strik *et al*., 2024). Further investigations in regards to clinical trials and safety upon long-term use is needed.

Soy and soy protein

In recent times, considerable attention has been given to soybeans as an excellent alternative to animal protein and also due to reports that it contains phytochemicals that prevent cancer and other chronic illnesses (Giri *et al*., 2012). Studies have identified at least 14 phytochemicals including flavonoids, coumarins, phenolics, phytic acid and carotenoids, all of which are involved in cancer prevention (Chandrasekara *et al.,* 2016). Furthermore, oligosaccharides, dietary fibre and protease inhibitors contained in soybeans are also known to exhibit similar physiological functions (Capuano, 2017).

Various anticancer compounds present in soybeans have been seen to suppress breast cancer cell proliferation with some combinations yielding a synergistic effect (Kojima-Yuasa *et al*., 2015). In vitro studies

using MCF-7 and MDA-MB-231 human breast cancer cells evaluated 12 bioactive compounds/molecules in soy protein including isoflavones, genistin, trypsin inhibitors, saponin, lectin, lunasin, daidzein and β-sitosterol. These compounds were assessed for antiproliferative action against human breast cancer cells. Results showed that the compounds enhanced the phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) by decreasing the phosphoinositide 3-kinase (PI3K) / Akt protein kinase B / mammalian target of rapamycin (mTOR) pathway. AMPK activation led to a regulation of cell cycle and inhibition of protein synthesis all of which resulted in suppression of tumour cell invasion and migration. Synergistic effects between genistin and daidzein were found to substantially increase proliferation of AMPK in MCF-7 cells as well as between β-sitosterol and genistin in MDA-MB-231 cells. The results from this study demonstrated that bioactive compounds in soybeans have a synergistic effect that could inhibit breast cancer cell proliferation (Zhu *et al.,* 2018)

Studies have shown that lunasin, a bioactive peptide isolated from soybean also has chemopreventive effects (Mcconnell *et al.,* 2015). Lunasin effectively inhibits the proliferation of non-small cell lung cancer (NSCLC) in H661 cell lines (Mcconnell *et al.,* 2015). Another study carried by Hao et al., (2020), showed significant inhibitory effects of lunasin on human breast cancer cells with inhibitory rates of lunasin extracted from wild type and transgenic soybeans being 23.8% and 43% respectively (Hao *et al.,* 2020). Results from a study using 40 and 80 μM concentrations of lunasin showed significant increase in apoptosis of HCT-116 colorectal cancer cell lines as a result of an increase in the expression of caspase-3 protein and inhibiting tumour-genesis (Fernandez-Tome *et al.,* 2020). The anti-cancer research on soybean proteins and peptides has shown that various compounds detected in soybean can inhibit cell proliferation or increase apoptosis in a number of cancer cell lines, these compounds could serve as active ingredients in the development of cancer chemotherapeutic drugs and may have major impact on prevention and treatment of cancer (Hu *et al.,* 2023). Thus, a high intake of soy and isoflavones have an inverse relationship with risk of cancer incidence and should be included in dietary plans for cancer prevention (Fan *et al*., 2022).

Vigorous intermittent physical activity

A large number of malignancies, including breast, endometrial, gall bladder, colon, oesophagus and pancreas are associated

with obesity (Gupta *et al*., 2015). Obesity is the second most common preventable cause of cancer and may be the most common preventable cause of cancer in non-smoking individuals, especially coupled with unhealthy eating and lack of physical activity (Sung *et al*., 2018). An increase in body weight is a contributing factor to an increase in the prevalence of cancer among young adults (Islami *et al*., 2019). Adiposopathic effects of obesity that aid the development of cancer include adipose tissue cytokine production such as tumour necrosis factor (TNF), interleukin-6, increased reactive oxygen species (ROS), which may damage cellular DNA, promote cell proliferation and gene mutations (Liou and Storz, 2010; Spyrou *et al*., 2018; Wlodarczyk and Nowicka, 2019). Unfortunately, no drug in clinical use today indicates treatment of both obesity and cancer (Lazarus *et al*., 2022).

About 4 min of daily vigorous intermittent physical activity such as bursts of very fast walking or stair climbing, was found to reduce physical activity-related cancer incidence by over 30%, which is especially beneficial to individuals who find it hard to practice traditional exercise (Stamatakis *et al*., 2023).

Nutrition and diet

Nutrition and diet are key factors in cancer prevention and treatment. As Hippocrates famously said, ‘Let food be thy medicine and medicine be thy food.’ An unbalanced diet can increase the risk of different cancers, while malnutrition can negatively impact the efficacy of different cancer treatments (Narimatsu and Yaguchi, 2022). Epidemiologic research over the last decade has identified genetic and lifestyle factors such as diet and nutrition, closely associated with cancer prevention. Over the years, the concept that dietary changes could potentially improve patient outcomes and response to treatment has attracted the attention of many patients. Growing understanding of the metabolism of cancer is emphasising the role that nutrition supply plays in tumour formation, development and treatment response. Cancers have a diverse multifactorial metabolic requirement largely influenced by the origin of tissue, microenvironment and genetics (Rakhmanovna, 2022). As a result, dietary modification must be tailored to the unique traits of each cancer and its course of therapy. This is a precision approach that necessitates a thorough comprehension of the mechanisms underlying the metabolic vulnerabilities of each disease (Tajan and Vousden, 2020).

Our growing knowledge of cancer metabolism has influenced the reasoning for maintaining a balance between fat and carbohydrates throughout cancer treatment. Glucose and fructose make up the majority of dietary carbs and sugar, with high fructose corn syrup consumption significantly rising in recent years (Tappy and Le, 2010). Several metabolic pathways that support proliferation and redox defence in cancer cells are supported through glycolyisis (Cairns *et al*., 2011), metabolism of fructose often results in uncontrolled glycolysis and fatty acid synthesis. In 2019, a report by Goncalves *et al*. showed dietary fructose contributed to the development of intestinal cancers in mice. Dietary supplementation with mannose, which reduces glycolysis in some malignancies, has been shown to impair tumour growth (Gonzalez *et al*., 2018). Increased glucose absorption and glycolysis has been observed in many cancers, these processes are assumed to support biomass creation, energy generation and antioxidant defence of these tumours. Restricting glycolysis through various dietary approaches including ketogenic diet and fasting can restrict cancer cell proliferation (Tajan and Vousden, 2020). Limiting circulating blood glucose levels by being on a keto diet or fasting decreases the availability of insulin and IGF-1. This process inhibits the activation of PI3K pathway, which is hyperactive in many malignancies that, enhances therapeutic response to PI3K inhibitors (Tajan and Vousden, 2020).

Low protein diets have been shown to impair cancer progression (Yin *et al*., 2018). Various observations in response to a low protein diet include regulation of IGF-1 levels, limitation of PI3K/AKT/mTOR signalling (Levine *et al*., 2014; Yin *et al*., 2018), induction of circulating FGF21 and activation of autophagy. These processes contribute to restrictions in cancer development although the mechanism by which this happens is still unclear. Rubio-Patino *et al*. in 2018 reported that a moderate reduction in protein intake induced endoplasmic reticulum stress in cancer cells. This prompted an induction of anti-tumour T-cell response. High levels of animal protein in a patient's diet seem to be more harmful than plant protein, this suggests that the precise amino acid content of the diet may be more important than the total amount of protein (Levine *et al*., 2014). In addition, consumption of certain vegetables that contain β-carotene such as carrots has been found to reduce cancer risk by about 20% across a wide range of geographical regions, exposure and cancer types (Ojobor *et al*., 2023). Thus, carrot consumption should be highly encouraged.

Appropriate diet and nutrition are needed for cancer patients and survivors in addition to pharmacological and surgical interventions to improve quality of life and treatment outcomes. This synergy of good nutrition and pharmacological treatment may be ideal even for cancers with unfavourable prognosis such as sarcomas and pancreatic cancer (Rovesti *et al*., 2021). A crucial factor to take to account is that dietary manipulation may trigger a systemic response that is not just restricted to the tumour but also other stromal players such as the immune system (Tajan and Vousden, 2020). A holistic approach to dietary restriction should be used to prevent development of cachexia and maintain a functional anti-tumour response.

Multivitamin supplement use

A significant number of diseases such as breast cancer are linked to vitamin D deficiency. Vitamin D, a fat-soluble vitamin is known for its ability to preserve the balance of calcium and phosphorus in tissues and cells of the human system. Serum levels of vitamin D ≥ 40.26 ng/ml ± 14.29 ng/ml, which can be achieved through dietary supplementation could produce a prophylactic effect against breast cancer (Torres *et al*., 2024). In a post hoc analysis of a randomized clinical trial, it was found out that patients who were p53 immunoreactive with digestive tract cancer and placed on vitamin D showed a significantly higher 5-year relapse-free survival rate as compared to placebo (Kanno *et al*., 2023). However, more clinical trials are needed in this field to access the benefits of multivitamin supplement use across different age and ethnic groups.

Vaccines

Seven viruses have repeatedly been associated with different forms of human cancer to date. They include Epstein-Barr virus (EBV), Kaposi's sarcoma herpesvirus (KSHV), high-risk (Human Papillomavirus) (HPV), Merkel cell polyomavirus (MCPV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), and human T-lymphotropic virus (HTLV-1), and infections are thought to be responsible for up to 20 % of cancer cases globally (Morales-Sánchez and Fuentes-Pananá, 2014). However, to date, only two vaccines have been developed to guard against two of these seven viruses; HBV and HPV, which have been implicated in hepatocellular carcinomas (HCC) and cervical cancer respectively (Petkar *et al*., 2023). Studies have reported that chronic HBV infection is associated with between 60 and 90 % of adult HCC and about 100 % of childhood HCC in areas where HBV infection is endemic (Chang, 2009), while persistent high-risk genital HPV infection

accounts for approximately 99.7 % of cases of cervical cancer, with over 600,000 new instances of cervical cancer recorded in 2020 (Okunade, 2020; Singh *et al*., 2023).

HBV vaccine, otherwise known as the 'first anti-cancer vaccine' is administered within 24 hours following birth, for all medically stable newborns that weigh at least 2 kg. When administering vaccinations before the age of six weeks, only single-component vaccines should be adopted for the birth dose, and 0 through 1, 2 through 6, and 6 through 18 months is the typical schedule. Due to possible decreased immunogenicity, the birth dose should not be included in the vaccination series for newborns weighing less than 2 kg. Instead, three more doses of the vaccine—for a total of four doses—should be given starting when the infant is one month old. The final dose should be given to infants whose mothers test positive for HBsAg by the age of six months, but not earlier than 24 weeks. All children and adolescents up to 18 years, not already vaccinated, should be administered a 3-dose series at 0, 1 and 6 months. Adults not vaccinated and at risk for or requesting protection from HBV infection can be administered a 3-dose series at 0, 1 and 6 months. Over 90 % of infants, children, adolescents, and healthy adults develop protective antibody response following the complete series, which is effective in preventing infection and subsequently, cancer (Haber, 2021).

Gardasil 9®, a 9-valent recombinant protein subunit HPV vaccine (9vHPV) is licensed for use in the United States, and it prevents infection with high-risk HPV types 16 and 18. These are HPV types that cause most cervical cancers. Regular vaccination is suggested for females and males at age 11 or 12 years (minimum age 9 years) or a catch-up vaccination is recommended for all persons not sufficiently vaccinated through age 26 years. However, it is not licensed for adults over 45 years. HPV vaccination schedule could either be a 2-dose series (0, 6–12month schedule; minimum interval of 5 months) or 3-dose regimen (0, 1–2, 6-month schedule). It has a high vaccine efficacy, with almost 100 % of recipients reported to develop an antibody response to targeted HPV types within four weeks after completing the regimen. However, there was no evidence of potency against disease caused by vaccine types with which patients were infected at the time of vaccination, but previous infection with one HPV type did not lessen the potency of the vaccine against other vaccine HPV types (Meites *et al*., 2021).

Conclusion

The increase in cancer incidence and mortality especially in low- and middle-income countries is a growing concern which needs to be addressed. The fact that a large number of these patients cannot afford their medications means prevention measures for this menace known as 'cancer' has to be exploited and also integrated alongside conventional cancer therapy. Furthermore, there is a clear gap in clinical trials involving repurposed drugs with already known safety profiles that have promising anti-neoplastic effects. This gap is an opportunity for researchers and research institutions in developing countries like Nigeria to delve into in order to develop cheaper alternatives for chemoprevention and treatment of cancer. Thus, educating policy makers and the public about measures that can relieve the burden on patients and the society incurred by cancer therapy is crucial.

Conflict of interests

There is no conflict of interests. No external financial support was obtained for this study.

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