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Phytochemicals in Cancer Management

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Abstract

The phytochemicals compounds found in plants are responsible for their colour, taste, and aroma of many foods. Over and above these attributes, emerging evidence suggests that they protect us from environmental and ingested carcinogens by arming antioxidant enzymes, enhancing DNA repair pathways, reducing chronic inflammation, and directly affecting the biological processes that underlie the fundamental hallmarks of cancer progression and metastasis. It is not a surprise, then, that the World Cancer Research Fund (WCRF) and other academic bodies report that individuals eating phytochemical-rich foods have a lower risk of cancer or relapse after treatments. The debate lies in whether concentrating these into nutritional supplements or topical creams can boost their health attributes without causing significant adverse effects. One notable randomised controlled trial has demonstrated benefits of a polyphenol-rich nutritional supplement for men with prostate cancer, another Randomised Controlled Trial (RCT) used a polyphenolic-rich topical balm to prevent distressing chemotherapy induced nail loss but, considering their potential benefits, there is a shortage of robust RCTs. This international evidence reviews highlights significant RCTs relating to cancer, their probable mechanisms of action and scope for future research.

Key words: Cancer; Diet; Phytochemicals; Polyphenols

Introduction

An increasing number of well-conducted studies are linking higher intake of phytochemical-rich foods with lower risks of chronic disorders ranging from arthritis to Type 2 Diabetes Mellitus (T2DM), as well as a lower risk of cancer and its relapse after initial treatments [1-3]. Of the numerous subcategories of phytochemicals, one of the largest and most well-researched groups is the polyphenols (Table 1). The average total dietary intake of polyphenols is reported to be over 1g per day, which is up to ten times higher than that of all other classes of phytochemicals [4]. Laboratory experiments have elucidated several anticancer mechanisms of action for phytochemicals, which might explain their benefits for patients both before and after cancer. Cohort studies correlating dietary patterns with disease outcomes provide useful insights, but scientific credibility is diluted by multiple causative factors in food and other lifestyle factors. Prospective clinical studies increasing dietary intake of certain polyphenol-rich foods are difficult to design and control, so most studies evaluate the pros and cons of concentrating phytochemicals into nutritional supplements in an attempt to further harness their health benefits. Nutritional supplements appear to be popular with cancer patients despite most of them not undergoing scientific evaluation [5-6]. This review provides up-to-date information to aid communication between patients and healthcare providers on the rationale, benefits and risks of increasing intake of phytochemical-rich foods and supplements.

Polyphenols
1. Flavonoids • Flavonols: quercetin, kaempferol (onions, kale, leeks, broccoli, buckwheat, red grapes, apples) • Flavones: apigenin, luteolin (celery, herbs, parsley, chamomile, rooibos tea, capsicum pepper) • Isoflavones: genistein, daidzein, glycitein (soya, beans, chick peas, alfalfa, peanuts) • Flavanones: naringenin, hesperitin (citrus fruit) • Anthocyanidins(red grapes, blueberries, cherries, strawberries, blackberries, tea) • Flavan-3-ols (tannins): catechins, epicatechin, epigallocatechin gallate (tea, chocolate,) • Flavanolols: silymarin, silibinin, aromadedrin (milk thistle, red onions) • Dihydrochalcones: phloridzin, aspalathin (apples, rooibos tea)
2. Phenolic acids
• Hydrobenzoic acids: gallic acid, ellagic acid, vanillic acid (rhubarb, grape seed, raspberries, blackberries, pomegranate, vanilla, tea) • Hydroxycinnamic acids: ferulic acid, P-coumaric acid, caffeic acid, sinapic acid (wheat bran, cinnamon, coffee, kiwi fruit, plums, blueberries)
1. Other non-flavonoid polyphenols
• Other tannins (cereals, fruits, berries, beans, nuts, wine, cocoa) • Curcuminoids: curcumin (turmeric) • Stilbenes: cinnamic acid, resveratrol (grapes, wine, blueberries, peanuts, raspberries) • Lignans: secoisolariciresinol, enterolactone, sesamin (grains, flaxseed, sesame seeds)
Terpenoids
1. Carotenoid terpenoids
• Alpha, beta and gamma carotene (sweet potato, carrots, pumpkin, kale) • Lutein (corn, eggs, kale, spinach, red pepper, pumpkin, oranges, rhubarb, plum, mango, papaya) • Zeaxanthin (corn, eggs, kale, spinach, red pepper, pumpkin, oranges) • Lycopene (tomatoes watermelon, pink grapefruit, guava, papaya) Astaxanthin (salmon, shrimp, krill, crab)
2. Non-carotenoid terpenoids
• Saponins (chickpeas, soya beans) • Limonene (the rind of citrus fruits) • Perillyl Alcohol (cherries, caraway seeds, mint) • Phytosterols: natural cholesterols, siosterol, stigmasterol, campesterol (vegetable oils, cereal grains, nuts, shoots, seeds and their oils, whole grains, legumes) • Ursolic acid (apples, cranberries, prunes, peppermint, oregano, thyme) • Ginkgolide and bilobalide (Ginkgo biloba)
3. Thiols
• Glucosinolates: isothiocyanates(sulforaphane) and dithiolthiones (cruciferous vegetables such as broccoli, asparagus, Brussel sprouts, cauliflower, horseradish, radish and mustard) • Allylic sulfides: allicin and S-allyl cysteine (garlic, leeks, onions) • Indoles: Indole-3-carbinol (broccoli, Brussel sprouts)
4. Other phytochemicals
• Betaines found in beetroot • Chlorophylls found in green leafy vegetables • Capsaicin found in chilli • Peperinefound in black peppers

Table1: Classification of phytochemicals and notable rich food sources [7-10]

Classification

There are three major groups of phytochemicals**:** the polyphenols, which can be subcategorized as the flavonoids, phenolic acids, and other non-flavonoid polyphenolsthe terpenoids, which can be subcategorized as the carotenoids and non-carotenoid terpenoidsand the thiols, which include the glucosinolates, allylic sulfides,and non-sulphur containing indoles [7-11](Table 1). Other phytochemical groups have been classified within a miscellaneous category (Table 1), some members of which also possess nutritional benefits and properties, including the betaines, chlorophylls, and capsaicin.

Clinical Evidence for a Link between Phytochemical intake and Reduced Cancer Risk

Most of the evidence for the benefits of phytochemicals in cancer prevention stems from well-conducted cohort studies which have linked a higher intake of phytochemical-rich foods, such as vegetables, fruit, legumes, nuts, herbs, and spices, with a lower incidence of cancer [1,3]. Although some earlier studies do not find an association, more recent studies do [12,13,14]. Of note, higher intake of carotenoids, found in leafy green vegetables and carrots, has been observed to have a significant dose-response relationship with reduced breast cancer risk in a meta-analysis pooling data from prospective cohort studies [15]. Studies based on questionnaires assessing intake of phytochemical-rich foods and serum levels of biomarkers have also demonstrated associations between high carotenoid intake and lower risks of ovarian and pancreatic cancers [16-18]. Intake of cruciferous vegetables such as cabbage, cauliflower, Brussel sprouts, radishes, and broccoli have been associated with a lower prostate cancer risk [19], as have foods rich in isoflavones such as pulses and soy products [20-22] and lycopene-rich colourful fruits and tomatoes [23]. Foods with abundant levels of flavonoids such as onions, rich in quercetin, have been associated in particular with are reduced incidence of cancers arising in the lung, especially among smoker [24,25]. The anthoxanthins in dark chocolate have been reported to be associated with a lower risk of colon cancer [26], and evidence indicates that higher green tea intake lowers the risk of breast, prostate, ovarian and oesophageal cancers, particularly among smokers and alcoholics [27,28]. Finally, higher coffee intake has been shown to be associated with reduced risks of both non-melanoma skin cancers and melanoma, even after controlling for confounding factors such as ultraviolet radiation exposure, body mass index, age, sex, physical activity, alcohol intake and smoking history [29,30].

Clinical Evidence for a Link between Phytochemical Intake and Reduced Cancer Recurrence

A number of studies have demonstrated that the benefits of consuming phytochemical-rich foods do not stop after a diagnosis of cancer. For example, breast cancer survivors who regularly consumed more than the government-recommended five portions of fruit and vegetables a day and participated in regular physical activity, had a significantly lower risk of breast cancer recurrence than those who did not [31,32]. In another study, women with breast cancer who had the highest serum lignan levels, reflecting good intake of legumes, cereals, cruciferous vegetables and soy, were reported to have better overall survival than those with the lowest levels [33]. A lignan and polyphenol-rich diet has also been associated with a lower colorectal cancer relapse rate [34].

The Shanghai Breast Cancer Survival Study, a large cohort study of 5,042 breast cancer survivors in China, demonstrated that women with the highest intake of the phytoestrogenicpolyphenols isoflavone and flavanone, found in soya and other beans, had a significantly decreased risk of breast cancer recurrence and death from any cause compared to those with the lowest intake at a median follow-up of 4 years [35,36]. Similar findings have been observed for high intake of green tea after breast cancer [37] and colorectal cancer [34]. High intake of green tea extract in a phase II trial of 42 chronic lymphocytic leukaemia patients was reported to produce a sustained, clinically significant decrease in the abnormal absolute lymphocyte count in 30% of patients [38]. Providing supplements of the phytochemicals rich in green tea to men with prostate cancer has been associated with a reduction in levels of serum Prostate-Specific Antigen (PSA), a marker of prostate gland disease used to monitor prostate cancer [39]. A slowing of PSA progression has similarly been observed in other interventional studies of phytochemical-rich foods for prostate cancer, most notably a Randomized Controlled Trial (RCT) studying an intensive lifestyle program intervention that included a vegan diet supplemented with phytochemical-rich soy products [40], and a phase II clinical trial of pomegranate juice (8 ounces/day) [41].

Individuals who have been treated for Squamous Cell Carcinoma (SCC) of the skin have a high risk of developing further skin lesions due to ongoing sun damage. A prospective study conducted in an Australian community reported that the highest levels of dietary intake of lutein and zeaxanthin-rich foods ofter an initial diagnosis of SCC, such as leafy green and yellow vegetables, were associated with a significantly reduced incidence of new cancer formation compared with the lowest levels of intake [42].

A number of other studies evaluating the impact of high intake of dietary phytochemicals after cancer diagnosis are currently underway, including the UK's DietCompLyf prospective cohort study, which is measuring serum polyphenol levels and recording dietary patterns of3, 159 women treated for breast cancer [43].

The likely Anticancer Mechanisms of Phytochemicals

The biochemical mechanisms through which phytochemicals exert their influence on cancer pathways are wide-ranging and still being explored. In terms of cancer prevention, a commonly cited mechanism is the direct antioxidant activity of phytochemicals, elicited through direct free radical absorption. The ability of phytochemicals to protect DNA from ingested or environmental

carcinogens, however, is likely to be mainly indirect, via their enhancement of the natural antioxidant enzymes and pathways in the body. Laboratory studies have shown that phytochemicals activate Nrf2, a transcription factor which switches on the genes that code for detoxification enzymes such as Super Oxide Dismutase (SOD), catalyse, and glutathione [44-46]. Furthermore, phytochemicals, particularly members of the thiol class such as sulforaphane, have been shown to exert protective effects by inhibiting the activity of enzymes which convert procarcinogens to their active, DNA-damaging carcinogen forms [44,47].

Practical evidence of the antioxidant and anticancer properties of phytochemicals has been obtained from a number of laboratory and animal studies involving common carcinogens. One study first demonstrated that chronic exposure to triclocarban *in vitro*, a chemical commonly found in household detergents, resulted in progressive mutation of noncancerous human breast cells to pre-malignant cells. The researchers then found that co-exposure of the triclocarban-exposed cells to cur cumin significantly reduced the amount and rate of carcinogenesis, as evidenced by decreases in cell proliferation and DNA damage among other end points [48]. In animal studies, rats exposed to cigarette smoke and then given indole-3-carbinol have been found to have a lower lung cancer development rate than those given a standard diet [49], while quercetin supplementation of mouse models of benzo(a)pyrene-induced lung cancer has been associated with attenuation of the decreases in antioxidant enzymes, including SOD and catalase, induced by benzo(a)pyrene [50]. Quercetin anticancer effects exhibited via significant decreases in oxidative stress have also been demonstrated in rat models of *N*-nitrosodiethylamine-induced liver cancer [51]. The antioxidant properties of betalain and other pigments in beetroot have been reported in several animal studies [52, 53]. Most notably, in one study, rats were randomly allocated to either a normal diet or a diet supplemented with dried beetroot extract. The rats were then administered carbon tetrachloride, a well-established carcinogen and reactive oxygen and nitrogen species (RONS) generator. The rats pre-treated with the beetroot were found to express significantly lower levels of lipid per oxidation, a marker of oxidative damage, than those which were not [54].

There is also evidence from clinical studies that phytochemicals have antioxidant effects in humans. For example, in one study, volunteers who ate a diet rich in quercetin and kaempferol were found on serum and urine analysis to have higher urinary concentrations of these polyphenols and improved SOD activity [55]. Eating a meal of onions has been found to increase subjects' serum levels of quercetin, indicating efficient absorption, and decrease urinary levels of 8-hydroxy-2'-deoxyguanosine, a marker of oxidative stress to DNA, four hours after ingestion of the meal [56,57]. Finally, aclinical study carried out in Singapore Chinese reported a significant correlation between increased consumption of cruciferous vegetables, rich in indole-3-carbinol, and decreased urinary levels of metabolites of a tobacco-specific lung carcinogen [58].

Some phytochemicals have anti-inflammatory properties. Although an inflammatory response is an important part of a healthy innate immunity, persistent low-grade increased chronic inflammatory activity is associated with age-related diseases such as Alzheimer's disease and atherosclerosis [59,60]. Higher levels of inflammatory markers have also been found to be associated with cancer incidence, more advanced cancers at presentation and an increased risk of cancer-specific mortality [61-63]. Markers of chronic inflammation are higher among individuals who are overweight, sedentary, those with poor diets, type II diabetes and the elderly [64,65]. One reason for this stems from overcompensation of an ailing immune system trying to maintain immunosenescence [65,66]. In these groups, Poor InterLeukin (IL)-2 production leads to a decreased cytotoxic capacity of NK and T lymphocytes on a 'per cell' basis. To compensate for this, higher levels of inflammatory biomarkers such as C reactive protein, Tumour Necrosis Factor (TNF), IL-6, cytokine antagonists and acute phase proteins are produced which increase concentrations of NK cells and T cells and these transcription factors regulate more than 150 genes involved in mechanisms of cell survival, inflammation, and cancer development [62-65].Numerous phytochemicals have been shown to inhibit NF-kappa B signalling *in vitro*, particularly the green tea polyphenol Epigallocatechin-3-Gallate (EGCG), quercetin, curcumin, caffeic acid, and caffeic acid phenethylester [67-69].Other anti-inflammatory mechanism of phytochemicals involve the prostaglandin and cox-2 pathways. Chronically increased overproduction of prostaglandins, generated via COX-2, has been implicated in cancer progression, apoptosis, invasion, angiogenesis and metastases [70-72]. Anti-inflammatory drugs and salicylates found in painkillers and fresh vegetables have been shown to reduce COX-2 activation of prostaglandins which could explain their reported anticancer properties [73,74].

In vitro laboratory studies have also demonstrated that phytochemicals can modulate cellular and signalling events fundamental to the growth, invasion, and metastasis of cancer cells [44]. For example, pomegranate extract, rich in the polyphenolellagic acid, has been shown to directly inhibit cell growth and induce apoptosis in androgen-sensitive and aggressive human prostate cancer cells [75,76]. Pomegranate juice and its phytochemical components have also been reported to inhibit processes underlying cancer metastasis in a study involving breast cancer cell lines. Pomegranate juice inhibited growth of the breast cancer cells, increased cancer cell adhesion, and decreased cancer cell migration, but did not affect normal cells [77]. Furthermore, pomegranate juice was found to inhibit chemo taxis, the process by which breast cancer cells are attracted to a chemokine factor in the bone [77]. Curcumin has been found to slow cancer cell growth through several mechanisms, including blocking the cell cycle, increasing the rate of apoptosis, and preventing the invasion and migration of cancer cells [78-83]. Curcumin has also been found to halt the growth of stem cells that give rise to breast cancer, without causing toxicity to differentiated cells [84]. Curcumin has been shown to modu-

late miRNA expression in cancer, leading to a reduced expression of the anti-apoptotic Bcl-2protein in breast cancer cells [85], and stabilisation of a tumour suppressor gene in colorectal cancer cell lines [86]. Green tea, rich in EGCG, has been found to impede processes that promote cancer cell proliferation by inhibiting DNA synthesis, cellular de-differentiation, and angiogenesis [87-92]. EGCG has also been shown to block ornithine decarboxylase, an enzyme which signals cells to proliferate faster and bypass apoptosis [93,94]. Resveratrol has demonstrated epigenetic regulatory properties which influence cell proliferation, survival, and apoptosis in prostate cancer by global modulation of gene expression through deacetylation of FOXO transcription factors [95]. Caffeic acid phenethyl ester, besides inhibiting NF-kappaB signaling, has also been shown to inhibit cell motility *in vitro* and inhibit metastasis of tumor models *in vivo* [96,97]. Luteolin has been shown in *in vitro* studies to inhibit tumor growth and metastasis, as well as the Epithelial-Mesenchymal Transition (EMT), a basic biological process underlying cancer initiation and development [98,99].

The phytoestrogenic polyphenols have hormonal properties that potentially influence cancers expressing oestrogen or androgen receptors. Most notably, the isoflavones and lignans found in soy products, legumes, and some cruciferous vegetables can weakly bind to the oestrogen receptor without stimulating proliferation of the receptor-bearing cells, thus blocking the binding of more harmful oestrogens, including those produced endogenously, to these receptors [100]. This may be the mechanism that at least partially underlies the results of clinical studies such as the previously mentioned Shanghai Breast Cancer Survival Study, in which women with the highest intake of isoflavone and flavanone-rich foods had the greatest overall survival [35]. In men, phytoestrogenic compounds have been shown to affect 5alpha-reductase and lower endogenous testosterone levels [101]. This mechanism partially explains why men who regularly eat soy, particularly non-fermented products such as tofu, have a lower risk of prostate cancer [102].

Polyphenols can also exert indirect influences on cancer development and progression by supporting or affecting other physical and mental functions. For example, a well-conducted RCT of 56 individuals with major depressive disorder reported that regular intake of curcumin (500 mg twice daily) was significantly more effective than placebo in improving depression-related symptoms after 4 weeks of treatment [103]. This result is important as depression after cancer treatments has been linked to reduced overall survival [104,105]. Increased dietary polyphenol intake has also been associated with improvements in fatigue [106], urinary infections [107], and arthralgia [108], all of which are adverse effects that often reduce patients' motivation and ability to be physically active after cancer treatments. Polyphenols thus not only exert beneficial effects in directly reducing these adverse effects, but also improve patients' ability to exercise more and reap the benefits of regular physical activity, such as reduced cancer relapse or recurrence rates and better quality of life [109,110].

An increasing body of evidence is demonstrating important advantages of dietary polyphenols for preventing and mitigating the adverse consequences of T2DM, which include cardiovascular disease and cancer [111,113]. A large prospective study of 1,111 T2DM case-control pairs selected from the Nurses' Health Study (NHS) and the Nurses' Health Study (NHS) II investigated the urinary excretion of eight polyphenol metabolites, and found that high intake of flavanones and flavonols, as well as the phenolic acid caffeic acid, was linked to a lower incidence of T2DM [114]. A study of 12,611 incident cases of T2DM across the NHS, NHS II, and Health Professionals Follow-Up Study found that a higher consumption of anthocyanins and anthocyanin-rich fruit was associated with a lower risk of T2DM [113]. Furthermore, two clinical studies have reported that the consumption of at least one apple a day, a dietary source rich in flavonoids, was associated with a lower risk of developing [111,113]. Finally, one prospective study has reported that the intake of polyphenols, especially the large polymeric type of condensed tannins found in legumes, was negatively correlated with the glycaemic index in both normal and diabetic participants, with the polyphenols appearing to be at least partly responsible for the reduced glycaemic response to simultaneously ingested carbohydrate foods [115].

The anti-diabetic effects of polyphenols may in part be related to the effects of the pulp and fibre often present in polyphenol-rich foods on slowing gastric emptying [112-114], [116-118]. In addition, one laboratory study reported that glucose transport in gut cells was directly inhibitedby flavonoid glycosides and non-glycosylated polyphenols such as EGCG [119]. Other *in vitro* and animal studies have reported that polyphenols may exert their anti-diabetic effects through mechanisms including inhibition ofthe production of α-amylase and α-glucosidase, reduction of hepatic glucose output, stimulation of insulin secretion and enhancement of insulin-dependent glucose uptake, and activation of 5' Adenosine Mono Phosphate-Activated Protein Kinase (AMPK) [120].

Type 2 diabetic patients have higher serum insulin levels than non-diabetics, as the pancreas produces more insulin to try to overcome the cellular insulin resistance that characterises T2DM. Hyper insulin is an independent risk factor for cancer development, related to increased insulin receptor stimulation on cancer cells [121]. In addition, hyper glycaemia-related oxidative stress and low-grade chronic inflammation, both associated with diabetes, promote malignant transformation [122,123]. It is not surprising, therefore, that several studies, including a large cohort study involving over one million people in Australia, have established significant links between T2DMand cancer incidence or mortality, including cancers of the colon, pancreas liver, uterus, kidney, thyroid, gallbladder, and leukaemia's [124,125]. Likewise, in the UK, a study of 62,809 patients with diabetes found them to have higher risks of colon and pancreatic cancer compared to a similar population without diabetes, especially if the diabetic patients were also obese [126]. Based on these data and findings, the American Dia-

betes Association and the American Cancer Society have issued a consensus report stating that T2DMconfers a two-fold higher risk for cancers of the liver, pancreas, and endometrium, and a 1.5-fold higher risk for cancers of the colon and rectum, breast, and bladder [116].

Benefits and Risks of Increase Dietary Phytochemicals?

A qualified nutritionist or dietitiancan advise on how to add more phytochemicals to every meal within a sustainable diet plan,tailored to the individual's needs and tastes, using herbs, spices, teas, vegetables, and fruits. In addition, numerous cooking tips and recipes are now readily available onlinefrom reliable sources, such as the Penny Brohn UK website (www.pennybrohn.org.uk/), a charity supporting those affected by cancer in living well,and the Cancernetblog, which provides regularmeal options, including the ingredients involved, the rationale for their health benefits, and videos showing how they are prepared and cooked [127].

There are several methods for increasing dietary phytochemical intake. Juicing and smoothies in moderation are helpful, but consumption of the whole fruit or vegetable is preferable, as methods which removethe bulk will increase the glycaemic index and free sugar content. Concentrating phytochemical-rich whole foods into a capsule or pill is a convenient way to supplement individuals with poor diets, or to further enhance the nutritional benefits in those whosediets are already adequate. It is certainly easier to conduct prospective interventional studies with supplements, as the quantity and quality of specifical substances can be controlled more precisely. This allows studies to allocate participants to arms involving increased intake of phytochemicals above the dietary average in order to test the hypothesis that phytochemical-rich foods have anticancer effects, and that increasing their intake may thus enhance their benefits. Many People Living With And Beyond Cancer (PLWBC) are certainly attracted to the potential health benefits of food supplements,as over 60% report regular intake [5,6].

Whole food supplements must be segregated from supplements which containextracted minerals and vitamins, as the overall evidence for the beneficial effects of the latter for individuals with relatively normal nutritional status is not encouraging. Whole food supplements are made from concentrated whole foods, and thus contain the natural combination of nutrients and other components present in the original whole food, in contrast to mineral, vitamin, or other extracted nutrient supplements which contain only those extracted nutrients.However, some specific extracted mineral and vitamin supplements have shown benefits in various clinical studies. For example, a recent meta-analysis reported that women who took vitamin C supplements or increased their dietary intake of vitamin C by >100 mg/day after their breast cancer diagnoses had significantly reduced risks of both breast cancer-specific and total mortality [128]. An RCT conducted in France studying a daily capsule supplement of a combination of ascorbic acid (120 mg), vitamin E (30 mg), beta-carotene (6 mg), selenium (100 μg), and zinc (20 mg) found no significant reduction in all-cause mortality or total cancer incidence compared to placebo at 7.5 years of follow-up. However, sex-stratified analysis revealed significant reductions in these clinical endpoints in men, but not in women, and further subgroup analyses in men found a reduction in the risk of prostate cancer with supplementation [129,130]. In another interventional trial, four different combinations of daily mineral and vitamin supplements at doses ranging from one to two times the US Recommended Daily Allowances were administered to 29,584 adults in Linxian, China, at a time when its population was known to have widespread micronutrient deficiencies. The study found a reduced risk of gastro esophageal cancer after 5 years of supplementation for the group receiving supplementation with beta-carotene, vitamin E, and selenium, compared to those receiving the other combinations of nutrients [131].

Most other clinical studies of supplements of vitamins, minerals, and extracted nutrients, however, have not shown beneficial effects before or after cancer diagnosis, and some report associations with increased risks of cancer. For example, the Beta-Carotene and Retinol Efficacy Trial (CARET) found that daily supplementation of a combination of beta-carotene (30 mg) and vitamin A (25,000 IU retinyl palmitate) was associated with an increased risk of lung cancer compared to placebo [132]. The Health Professionals Follow-Up Study (HPFS), which followed the lifestyle habits of 51,529 male professionals for more than 15 years, found that men who took very high doses of supplemental zinc (>100mg/day), or took it for long durations (≥10 years), were more than twice as likely to develop advanced prostate cancer than men who did not take zinc supplements [133]. A subsequent prospective study followed up the 4,459 men initially diagnosed with prostate cancer in the HPFS, and found that selenium supplementation of ≥140 μg/day after diagnosis was associated with a 2.6-fold greater risk of prostate cancer mortality compared with non-users of supplements [134]. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) randomised 43,887 men to one of four groups, selenium supplementation alone (200μg/day), vitamin E supplementation alone (400IU/day of either rac-alpha-tocopheryl acetate, a supplementation containing both, or placebo and demonstrated a significantly increased risk of prostate cancer with vitamin E supplementation compared with the other three groups after at least 7 years of follow-up [135]. The negative effect of beta-carotene supplements seen in the CARET study was also found in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, where 20 mg/day of beta-carotene for 5-8 years was associated with an increased risk of lung cancer [136]. Interestingly, a subsequent analysis of the results of the ATBC Study showed that men with low pre-supplementation serum levels of beta-carotene had a lower prostate cancer risk following supplementation, while those with high pre-supplementation serum levels of beta-carotene had a higher risk of prostate cancer following supplementation, particularly in smokers [137]. This U-shaped distribution of risk associ-

ated with low and high levels of a specific nutrient this also been observed in the European Prospective Investigation into Cancer and Nutrition (EPIC*)* Study, where those with folate-deficient diets and those with the highest intake of folate both had a higher risk of pancreatic cancer [138]. These findings from numerous RCTs have prompted organisations such as the National Cancer Institute to issue statements stating that long-term vitamin and mineral supplements should ideally only be taken to correct a known deficiency [139].

Studies which have evaluated the cancer risk-reducing effects of supplementation of extracted individual polyphenols have also not produced encouraging results. For example, findings of the benefits of lycopene or genistein taken alone for reducing prostate cancer risk in earlier reports have not been confirmed or replicated in subsequent studies [23,140-143]. Neither has regular intake of such individual polyphenols been associated with reduction in the risk of breast cancer [15,144]. Of more concern are the results ofan RCT from the Memorial Sloan-Kettering Cancer Center, which explored the effects of high-dose genistein supplementation (25.8g soy protein powder twice daily) for 30 days, or until surgery, in women with early-stage breast cancer. The high-dose genistein supplementation was found to induce changes in the expression of 21 genes, leading to a possibly adverse genetic expression profile in breast cancer. Furthermore, the addition of blood serum obtained from women in the supplementation group to laboratory tumor cells caused the tumor cells to proliferate faster and overexpress the tumourigenic growth factor receptor FGFR2 [145]. Based on this evidence, concentrating phytoestrogens into strong supplements is not currently recommended.

More recently, academic attention has turned towards the evaluation of dried and concentrated whole foods which contain an array of polyphenols and other phytochemicals. Reassuringly, no notable study of non-phytoestrogenic whole food supplements thus far has shown any detrimental effects on cancer outcomes, and some studies have demonstrated considerable benefits. For example, a randomised phase II dose-exploring study carried out at Johns Hopkins found that men taking either of two doses of a pomegranate extract supplement (1 g or 3 g) for 18 months experienced significant reduction in progression of PSA levels compared to the baseline PSA progression rate pre-treatment [146]. A phase II trial of a green tea concentrate supplement containing a standardized dose of EGCG (2000 mg per dose), administered twice daily to chronic lymphocytic leukemia patients for up to 6 months, found that the treatment was associated with a sustained and clinically significant decrease in the absolute lymphocyte count in 30% of patients [38]. A small study of men with prostate cancer scheduled for radical prostatectomy reported that daily administration of a green tea concentrate supplement containing 800 mg of EGCG (and a total of 1300mg of tea polyphenols) for several weeks, from initiation of the study until the scheduled prostatectomy, caused a significant reduction in the serum levels of PSA and several cancer-promoting growth factors compared to pre-study baseline levels [39]. In the large Vitamins and Lifestyle (VITAL) cohort study, intake of grape seed extract supplements was shown to be associated with a significantly reduced total risk of prostate cancer after 6 years of follow-up [143]. Another small crossover RCT found that a dietary supplement containing isoflavone-rich foods, including 62.5 mg of soy and 15 mg of lycopene among other phytochemicals and antioxidants, administered 4 times a day for treatment periods lasting 10 weeks, significantly delayed PSA progression compared to placebo in men with a history of prostate cancer who had received potentially curative therapies [147]. Interestingly, one of the most popular supplements, saw palmetto fruit extract*,* despite demonstrating beneficial effects in early small studies, has shown no benefits for improving the symptoms of benign prostatic hyperplasia, delaying PSA progression, or reducing prostate cancer risks larger observational or randomised interventional evaluations of its effects [148-151].

To date, the largest RCT analyzing the effects of phytochemical-rich whole food extracts on cancer risk has been the UK National Cancer Research Network Pomi-T Study [152]. This study combined four different dried foods (pomegranate, green tea, broccoli and turmeric) into a single tablet, taken 3 times a day, in order to provide a wide spectrum of synergistically-acting nutrients whilst avoiding over-consumption of any particular phytochemical. The trial involved 200 men with localised prostate cancer, managed with either active surveillance or watchful waiting. The results showed a statistically significant 63% reduction in median PSA progression rate at 6 months of intervention for the group randomised to the supplement compared to placebo. A further analysis of the men's MRI scans demonstrated that presence of disease, cancer size, and growth patterns on the scans correlated with PSA changes, providing support for the conclusion that the supplement was exerting beneficial effects not just on PSA levels, but on the disease, itself [7,152]. Furthermore, the supplement was well-tolerated, and there was no effect on testosterone levels. At the end of the study, significantly more men opted to remain on surveillance and continue with lifestyle and nutritional interventions, such as taking the food supplement, rather than proceed to expensive radiotherapy, surgery, or medical castration options, which can cause unpleasant adverse effects such as depression, hot flushes, weight gain, osteoporosis, and erectile dysfunction [7].

Polyphenols and Chemotherapy

There have been some concerns that polyphenols may interfere with oncology treatments, especially considering their antioxidant properties. The section above has highlighted that antioxidant properties are only one of the many mechanisms of action exerted by polyphenols. Moreover, polyphenols mainly enhance the production and action of antioxidant enzymes, rather than having a direct effect on free radical absorption, unlike other nutrients such as vitamins A and E [4, 46,153]. Most importantly, laboratory studies have reported that polyphenols exert direct anticancer

properties by helping to reduce excessive cell proliferation, de-differentiation, loss of cell adhesion, and metastasis, and supporting apoptosis [20,44,75-81,86,97,154]. It is not surprising, then, that several studies have actually found that polyphenols enhance the cytotoxic effects of chemotherapy, rather than impede it. For example, a two-fold greater anti-cancer efficacy of intravenous curcumin and docetaxol, a chemotherapy drug, compared with docetaxolalone, was reported in a transplanted xenograft mouse model of lung cancer, without an increase in damage to normal tissue [155]. Curcumin has also been found to enhance the effectiveness of cisplatin, another chemotherapy drug, by helping to reduce cell proliferation in a study of laryngeal carcinoma cancer stem cell model [81]. Another *in vitro* study reported that beetroot juice both promoted apoptosis of breast cancer cells after exposure of the cells to the cytotoxic chemotherapy agent doxorubicin, and protected normal cardiomyocytes, or heart muscle cells, from the toxic effects of doxorubicin [156].

These findings from laboratory studies are encouraging, but the true clinical potential of polyphenols and other phytochemicals in cancer can only be tested within large RCTs. Fortunately, there are currently over ten on-going studies registered with the National Institute of Health, US, and a number of studies are also ongoing in the UK. Notably, the Arthro-TRCT (Eudra CT number 2017-000201-20) is investigating whether a supplement made from a blend of polyphenol-rich foods could help to reduce joint pains and fatigue related to cancer treatments, and thus allow patients to achieve greater levels of physical activity.

Emerging evidence suggests some plant extracts may also have a role in preventing cutaneous toxicities of cancer treatments. Distressing nail damage (onycholysis) is common amongst patients receiving chemotherapy, especially taxanes, causing pain, disfigurement secondary infection and interference with activities of daily living [157]. One recent RCT (the UK poly balm study) explored the bioactive properties of a number African herbs including leleshwa, *Gaultheria procumbens*, *Lavandula officinalis*, *Eucalyptus globulus* and *Tarchonanthus camphoratus*. The phenolics and other phytochemical in these herbs have been reported to have moisturizing, anti-inflammatory, anti-microbial and anti-oxidant properties [158,159]. The participants on chemotherapy randomized to the investigational balm had little of no nail damage or discomfort compared to over 50% in the placebo group recorded with four different measures of toxicity and this difference was highly statistically significant [160]. It was correctly hypothesized, by the researchers, that the oils in the poly balm were sufficiently absorbed into the nail bed to prevent cracking and splitting, act as a local antidote to the chemotherapy, protecting the proliferating stem cells. In addition, their anti-microbial properties helped prevent secondary infection so overall keep the nail healthy and intact. The success of this trial opens up possibilities for topical preventative interventions for other skin conditions such as hand foot syndrome, hair loss and even within mouth washes.

Conclusion

There is increasingly convincing evidence to show that plant phytochemicals, particularly polyphenols, have significant health benefits for humans. Regular phytochemical intake is linked to a reduce risk of developing cancer and benefit patients living with and beyond cancer diagnosis and treatment. “Living Well” programmes are being introduced in the UK, largely driven by the National Cancer Survivorship Initiative and guidelines from influential organisations, and are beginning to highlight the importance of a regular intake of colourful variety of vegetables, fruits, legumes, nuts, herbs and spices to harness the beneficial effects of the numerous phytochemicals available through our food alongside other lifestyle factors. Going step further and concentrating phytochemical-rich foods into nutritional supplements or balms provides an opportunity to boost their beneficial effects. Although some studies of concentrated minerals, vitamins, and phytoestrogenic supplements have reported detrimental effects, there have been no RCTs reporting significant detrimental effects for whole, non-phytoestrogenic food supplements. Some RCT’s have reported significant advantages for these types of supplements in slowing cancer progression and preventing side effects of chemotherapy. Despite these potential benefits and reports that over 60% of cancer survivors take nutritional supplements, many oncologists are reluctant to discuss the pros and cons of taking such supplements with their patients. This reluctance is due in part to the lack of large, well-conducted RCTs exploring phytochemical-rich interventions, with a significant proportion of the evidence for the benefits of phytochemical supplementation arising from observational studies, which makes it difficult to assess causality [96,161]. Hopefully this trend will change, particularly following the success of the Pomi-T[7], and polybalm studies [160] together with forthcoming evidence from interventional studies being performed around the world.

Conflict of interest

Professor Thomas has received speaker’s fees from Helsinn Integrative Healthcare, Astra Zeneca and Novartis pharmaceuticals as well as travel grants from Bayer Pharmaceuticals. The other authors declare that they have no relevant conflicts of interest.

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