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Resveratrol and Malignancies

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Abstract

Carcinogenesis is a multifactorial process, frequently encompassing 3 stages: initiation, promotion and progression. It is characterized by multiple deviations from normal both at the cell and organism levels. Although most people have a small number of cells that present deviations from normal, most of those cells will not cause cancer. However, some will. What tips the balance between normal and abnormal is the subject of intense scientific research as well as unfounded speculations. Chronic inflammation is one of the risk factors for cancer. Resveratrol is consumed by the population as a dietary supplement in the hope of decreasing the risk of inflammation and cancer and other chronic diseases such as diabetes and vascular diseases. There is a discrepancy between the doses used in the animal studies showing that resveratrol decreases all three stages of carcinogenesis, and the doses ingested by the population either as supplements or in the diet. While there is health benefit from using high resveratrol doses, it might be also of practical and scientific benefit to focus future effort in understanding the effects of normal dietary resveratrol levels.

Keywords

Resveratrol; 3,4′,5-Trihydroxy-trans-stilbene; 5-[(1E)-2-(4-Hydroxyphenyl) ethenyl]-1,3-benzenediol; Stilbene; cancer; human

Introduction

According to the CDC, regarding incidence**,** the top 10 cancer sites (2007–2011) in males in the United States are: prostate, lung and bronchus, colon and rectum, urinary bladder, melanomas of the skin, non-Hodgkin lymphoma, kidney and renal pelvis, oral cavity and pharynx, leukemias, and pancreas. The top 10 cancer sites (2007–2011) in females in the United States are: breast, lung and bronchus, colon and rectum, corpus and uterus not

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

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otherwise specified (NOS), thyroid, non-Hodgkin lymphoma, melanomas of the skin, ovary, kidney and renal pelvis, and pancreas. In children (0–19 yrs. old), the invasive cancer with highest incidence rates are acute lymphocytic leukemia, brain and other nervous system, non-Hodgkin lymphoma, Hodgkin lymphoma, soft tissue, bones and joints, acute myeloid leukemia, kidney and renal pelvis. Some cancers, although their incidence rates do not reach the top 10, have death rates that are among the top 10: liver and intrahepatic bile duct, urinary bladder, `esophagus in men; and leukemias, brain and other nervous system, liver and intrahepatic bile duct in women.

Resveratrol is consumed by the population as chemopreventive agent. From the seminal paper published in Science in 1997 [1] till now, more than 7000 scientific papers were published on resveratrol (http://www.ncbi.nlm.nih.gov/pubmed/?term=resveratrol, as searched on 1/20/2015). The initial enthusiasm evolved into partial disappointment due to the awareness that resveratrol affects most of the known biochemical and signaling pathways [2, 3] and due to the high doses needed to elicit those cellular responses [2, 4 ••]. This review seeks to summarise the effects of resveratrol regarding the main human cancers and to propose a few new directions for resveratrol chemoprevention.

Resveratrol

Resveratrol is a polyphenol also known under the synonym names: 3,4′,5-Trihydroxy-trans-stilbene, or 5-[(1E)-2-(4-Hydroxyphenyl) ethenyl]-1,3-benzenediol. It is a dietary naturally occurring phytoalexin. Its main dietary sources in human diet are the skin and seeds of grapes, peanuts, mulberries [1]. It is also very abundant in the root of *Polygonum cuspidatum* [5 ••]. In an excellent review, Ma and Hu assess essential facts about resveratrol's fate across the gastro intestinal tract [4 ••]. They review the main publications showing that piceid, the 3-β-glucoside of resveratrol, the most abundant form of resveratrol in nature, is cleaved by intestinal flora to resveratrol and a sugar moiety. They also show low aqueous solubility of resveratrol and low bioavailability, however the low bioavailability is not due exclusively to low solubility [4 ••]. It is important to point out that although the bioavailability is low, resveratrol is nevertheless bioavailable following oral administration [2]. Resveratrol crosses the intestinal apical membrane due to its lipophilic nature, and in Caco-2 cells a transporter, SGLT1, was reported as being important especially for the transport of piceid which is hydrolysed to resveratrol in the epithelial cell [4 ••]. The low oral bioavailability of resveratrol is thought to be due to phase II metabolism in the enterocyte [4 ••]. However, there are expert opinions that this is not an impediment. The biological effects of resveratrol are also due to its metabolites [2]. MRP2 on apical side of enterocytes (transporting back into the intestinal lumen) and MRP3 on the basolateral side (transporting to the portal vein and lymph duct) are thought to be active in excreting the metabolites of resveratrol [4 ••]. The apical efflux from enterocytes might be the main cause of low bioavailability. The enterohepatic recycling of resveratrol is also important for bioavailability, but less studied. Resveratrol is present in serum and urine predominantly as glucuronide and sulfate conjugates [6].

Cancer, Inflammation and Resveratrol

Although the causes of cancer are multiple and not easy to classify, chronic inflammation is recognized as a leading risk factor. Chronic inflammation is a significant public health concern in Western populations. There are multiple causes and molecular mechanisms of chronic inflammation. There are genetic and metabolic factors but also dietary and environmental factors. Many people use resveratrol in order to prevent chronic inflammation and associated pathologies, such as cardiovascular diseases, metabolic syndrome and cancer. In fact the first discovered biological effect of resveratrol was its anti-inflammatory effect by modulating arachidonate metabolism [7] and inhibiting cyclooxygenase [1]. A plant rich in resveratrol, *Polygonum cuspidatum*, is highly used in Chinese medicine to treat inflammation and cancer as well as metabolic diseases [5 ••], and it is the main source of resveratrol for commercially available supplements. Resveratrol (in high doses) was rigorously demonstrated to hinder cancer initiation, promotion and progression in 1997 [1].

Is there evidence that resveratrol is relevant against human cancers?

After decades of research on resveratrol, and high hopes for its antitumor effects, there is still not a clear understanding of its effectiveness. Below we present just a few examples of studies on resveratrol for the main human cancers. Those examples show the broad range of cancer types in which resveratrol was tested, encompassing most of the prevalent cancers.

Colon and rectum cancers

Most clinical trials investigating the anticancer effects of resveratrol were in colon cancer.

In trial NCT00256334, resveratrol-containing freeze-dried grape powder (low dosages of resveratrol in combination with other bioactive components) can inhibit the Wnt pathway in vivo [8].

In NCT00578396 (phase 1), primary cell lines generated from resected colorectal tumor specimens were treated with mitomycin C and resveratrol and had greater up-regulation of p21(WAF1/CIP1) (which inhibits the cell cycle at G0/G1 and G2/M phases) compared with the cells treated with either agent alone [9].

There are also two other clinical trials with less information available so far. NCT00920803 (Phase 1) and NCT00433576 that assess resveratrol in treating patients with colorectal cancer that can be removed by surgery (Phase 1). In another clinical study performed in the United Kingdom, twenty patients with histologically confirmed colorectal cancer consumed eight daily doses of resveratrol at 0.5 or 1.0 g before surgical resection. Resveratrol and its metabolites: resveratrol-3-O-glucuronide, resveratrol-4′-O-glucuronide, resveratrol-3-O-sulfate, resveratrol-4′-O-sulfate, resveratrol sulfate glucuronide, and resveratrol disulfate were present in colorectal resection tissue. Resveratrol reduced cell proliferation by 5% [10].

Liver and intrahepatic bile duct, gastro intestinal cancers

There have been a couple of GI clinical trials: ACTRN12612001135808 and NCT01476592. In nonalcoholic fatty liver disease (NAFLD) patients, 3 g/day resveratrol for 8 weeks

increased levels of alanine and aspartate aminotransferases, markers of hepatic stress [11]. NAFLD is a risk factor for hepatocellular carcinoma. NCT01476592 is an active clinical trial assessing resveratrol's effects on notch-1 signaling in subjects with low grade gastrointestinal tumors. In a phase I randomized, double-blind pilot study performed in United Kingdom in patients with hepatic metastases, receiving 5.0 g micronized resveratrol (SRT501) daily for 14 days, it was found that this regimen was well tolerated and micronized SRT501 led to higher bioavailability than resveratrol. This regimen led to a significant increase in cleaved caspase-3, a marker of apoptosis, in malignant hepatic tissue [12].

Leukemias

The potential to use resveratrol in chronic myelogenous leukemia and Ph+ acute lymphoblastic leukemia as reviewed by Vakana and Platanias [13] showed that resveratrol activates the heterotrimeric AMP-activated protein kinase (AMPK) complex and JNK-dependent p62/SQSTM1. They also pointed out Puissant and collaborators' important finding that resveratrol has the potential to induce apoptosis in some imatinib resistant chronic myelogenous leukemia cells [14]. In the initial report of resveratrol's antitumor activity, Pezzuto and collaborators used HL-60 myelo-monocytic leukemia cells to show that resveratrol caused growth arrest and induction of differentiation (assessed by respiratory burst) [1]. Aggarwal and collaborators showed that resveratrol also suppressed colony-forming cell proliferation of fresh AML marrow cells from patients with newly diagnosed AML in a dose-dependent fashion [15].

Lymphoma

A population-based genetic association study showed correlation between mutations in AMPK subunit genes and the risk of non-Hodgkin lymphoma [16]. As resveratrol activates AMPK [13], there is hope that it has chemopreventive effects for lymphoma. In Hodgkin lymphoma (HL)-derived L-428 cells, resveratrol induces apoptosis by SIRT1 inhibition and FOXO3a hyperacetylation [17].

Multiple myeloma

NCT00920556 was a terminated Phase 2 study on multiple myeloma with 5 g/day SRT501 in 21 day cycles. It was a study of SRT501 (resveratrol) with bortezomib for patients with relapsed and or refractory multiple myeloma. It showed that the disease stabilization caused by bortezomib alone can prevent renal failure [18].

Brain and other nervous system cancers

In patient isolated glioma stem cells, resveratrol activates the p53/p21 pathway and suppresses Nanog [19 ••]. In medulloblastoma cell line, resveratrol with 5-Aza-dC inhibits metabolic activity [20].

Soft tissue cancers

Resveratrol inhibits rhabdomyosarcoma cell proliferation by causing S/G2 arrest and cyclin B downregulation, in a human embryonal rhabdomyosarcoma model [21]. Resveratrol

together with clofarabine inhibits mesothelioma MSTO-211H cell growth, Nrf2 activation and its target gene heme oxygenase-1 (HO-1) expression [22].

Bone and joint cancers

Using a bone cancer pain model, resveratrol was recently suggested to have analgesic effects by inhibiting the spinal glial activation and decreasing CX3CR1 [23].

Tyroid cancers

Resveratrol activates Notch1 signaling, induces differentiation (TTF1 and Pax8) and suppresses cell growth in anaplastic thyroid carcinoma [24].

Pancreatic cancer

In pancreatic cancer stem cells, resveratrol inhibited self – renewal capacity, migration and invasion, Nanog, SOX-2, c-Myc, Oct4 and ABCG2 (markers of pluripotency); Zeb-1, Slug and Snail (markers of epithelial-mesenchymal transition) [25].

Prostate cancer

NCT01317199 is a clinical trial lead by Johns Hopkins University which is estimated to be completed this year. It is a phase 1 and 2 clinical trial aiming to assess effects of two doses of “Muscadine Plus Grape Skin Extract” capsules on rising prostate-specific antigen levels in men following initial therapy for prostate cancer.

Breast cancer

NCT01370889 was completed. In overweight and obese postmenopausal women, 1 g/day resveratrol showed favorable effects on estrogen metabolism and a 10% increase in the concentrations of sex steroid hormone binding globulin, thus reducing the breast cancer risk factors in this population[26]. In MCF-10A cells, resveratrol prevented 17β-estradiol-induced decrease in SOD3, NQO1, Nrf2 mRNA levels [27].

The relationship between estrogen levels, persistent organic pollutants and resveratrol as modulators of cancer risk deserves special attention. In animal models it has been shown that gestational exposure to the xenobiotic 2,3,7,8-tetrachlorodibenzo-p-dioxin induces BRCA-1 promoter hypermethylation and reduces BRCA-1 expression in mammary tissue of the offspring [28]. Those effects have been shown to be prevented by resveratrol in the MCF-7 cell model [28]. Moreover aryl hydrocarbon receptor, also known as dioxin receptor, (AhR) has an important role in modulating the immune system [29–33]. Resveratrol was reported to inhibit breast cancer metastasis by inactivating the tumor-evoked regulatory B cells [34].

Remarks and new directions

AhR and NRF2 as inflammation- environment-diet molecular cross-roads

The main reason people take resveratrol is to prevent inflammation, a physiological response to an environmental or internal insult. The potential link between AhR as a modulator of immunity (inflammation) and response to xenobiotics on one hand and resveratrol activities

on the other hand is intriguing. Moreover, it is interesting to mention that the effect of resveratrol is frequently associated with upregulation or activation of Nrf2 [35–37]. Furthermore, resveratrol upregulates phase II metabolism enzymes (such as HO-1, NQO1) expression by increasing the transcriptional activity of Nrf2. Those phase II metabolism enzymes are also transcriptionally controlled by AhR via XRE in their promoters [38]. Moreover, many people taking resveratrol also take AhR – inducing agents, such as valproic acid as mood stabilizer, chemotherapy, and Gingko biloba. Additionally, we are all exposed to various AhR activating environmental pollutants. There are also dietary AhR antagonists such as genistein, kaempferol or EGCG. AhR is an important protein orchestrating stacking (resultant effect of more than one dietary supplement), drug- supplement or pollutant-supplement effects. Important players in inflammation are monocytes and macrophages and their vasculature interactions. A relatively novel AhR synthetic agonist, VAF347, is a low molecular weight, cell permeable compound that causes a number of anti-inflammatory responses *in vitro* and *in vivo* [39]. For example, it inhibits the development of $CD14^{+}CD11b^{+}$ monocytes from granulo-monocytic (GM stage) precursors [40]. Resveratrol is reported to decrease inflammation and improve vascular parameters. It would be of interest to elucidate in greater detail the contribution of AhR to resveratrol's effects and the collaboration of AhR with Nrf2, especially in the maintenance of homeostasis. It is an attractive hypothesis that low (dietary) to moderate (supplements) doses of resveratrol assist Nrf2 and AhR in maintaining homeostasis against environmental or inflammatory insults that otherwise might be tumor initiators. Due to the long effect time and multiparameter nature (including many confounding factors), it will be difficult to test this hypothesis.

Resveratrol in other clinical trials with relevance for cancer prevention

Although not directly investigating antitumor effects, some resveratrol studies are relevant to its possible anti-cancer effects or to improving the well being of cancer patients or survivors. The NCT01354977 clinical trial aims to assess the effect of resveratrol on age-related inflammation in humans, and although it does not directly assess cancer parameters, it asses a recognized risk factor. NCT01043939 assessed the effect of resveratrol rich grape juice in childhood cancer survivors. In another study, 200 mg/d resveratrol intake for 26 weeks in healthy older adults resulted in reductions in body weight and BMI and decreases in systolic and diastolic blood pressure associated with improvements in the integrity and functionality of the hippocampus [41]. In conclusion, there is encouraging data, both for potential antitumor effects as well as improving the wellbeing of patients and the general population.

A large number of clinical trials investigate the health promoting and therapeutic effects of resveratrol, however, it is noteworthy mentioning that the doses used in most of the clinical trials are much higher (at least 10 times higher) than the dose one person would ingest in the diet or by taking the label recommended dose of commercially available supplements. Moreover, taken in the diet, resveratrol is likely to have other nutrient-resveratrol interactions compared to being taken as a supplement.

Conclusions

There is a grey zone in the public perception and perhaps at a certain degree even in the scientific literature, between the high dose pharmacological effects of resveratrol (including its structural or functional analogues) and the effects of dietary resveratrol. We believe that both have their merits, but are clearly distinct. Some clinical studies investigate the effects of very high doses of resveratrol, aiming to assess its therapeutic role. Perhaps prospective studies assessing the intake of resveratrol supplements and consumption of foods rich in resveratrol on the one hand and assessing cancer incidence on the other hand, could clarify the association between resveratrol intake and cancer incidence and thus its chemopreventive role.

Regarding its molecular role, it appears that resveratrol, at least in high concentrations as used in most studies, affects most signaling and metabolic pathways. The shift in the perception that resveratrol directly regulates Sirt1 to the current accent on cAMP signaling [13, 42 ••] deserves reflection and points again to the need of studying the effect of lower doses. Historically resveratrol was intensely studied in the aging process as a direct activator of SIRT1. Its presence in red wine propelled it to headlines in newspapers. The controversy about the assay measuring the SIRT1 activity and the involvement of SIRT1 in aging led to a decrease in the enthusiasm level for resveratrol studies in general [43, 44]. This piece of modern science history points to the need for moderation in our interpretations of the scientific findings, avoiding both passionate desire of finding *elixir vitae*, “elixir of life”, and hasten dismissal of any health benefits of one natural compound once our utopian dreams were not met.

We regret it was not possible because of space limitations to cite all of the important work that has been reported in this broad and active field and apologize for omissions.

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