Dietary Oncopharmacognosy

Subjects: Nutrition & Dietetics

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While diet and nutrition are modifiable risk factors for many chronic and infectious diseases, their role in cancer prevention and control remains under investigation. The lack of clarity of some diet–cancer relationships reflects the ongoing debate about the relative contribution of genetic factors, environmental exposures, and replicative errors in stem cell division as determinate drivers of cancer risk. In addition, dietary guidance has often been based upon research assuming that the effects of diet and nutrition on carcinogenesis would be uniform across populations and for various tumor types arising in a specific organ, i.e., that one size fits all.

cancer prevention and control | dietary oncopharmacognosy | pharmacology | natural products

1. Introduction

Given the impact of diet and nutrition on many chronic and infectious disease processes, an expectation has existed for decades that similar effects would be observed for cancer [1][2]. Yet, despite a global effort to identify those linkages, the literature supporting diet's role in cancer development and progression has inconsistencies [3][4][5]. In addressing this conundrum, one recent *Nature* perspective calls for higher quality research in this arena [6]. This is undoubtedly needed. Similar to the World Health Organization's approach to addressing the relationship between obesity and cancer [7], the area of diet and nutrition in cancer requires a bottom-up (mechanistic) as well as a top-down (population to clinical studies) process to reframe key questions and identify high probability causal relationships at the interface of precision oncology and precision nutrition that can be translated to precision public health. Despite small-molecule inhibitor pharmaceuticals becoming a mainstay of cancer treatment, the paradigm has failed to seize the opportunity to leverage culinary medicine and exposure to food-derived small molecules to improve patient outcomes. Herein, researchers re-introduce two concepts from the mid-1970s: (1) targeting the entire process of carcinogenesis for treatment and (2) suppressing, inhibiting, and reversing any phase of the disease process from the generation of a cancer-initiated stem cell to cancer specific death after a cancer diagnosis [8][9]. The success of targeted treatment with small-molecule inhibitors of protein kinases, apoptosis evasion, immune suppression, and angiogenesis induction in reducing cancer deaths provides a framework for re-examining the role of diet and nutrition in cancer prevention. Researchers leverage the pioneering science that identified the origins of cancer driving mutations and emerging hallmarks of cancer to identify targets for precision nutrition: (1) the protein products of the genetic drivers of carcinogenesis [10][11][12][13] and (2) tissue-specific effects on the carcinogenic potential of cells bearing driver mutations within that tissue, i.e., "field effects" [14][15][16].

2. Definitions

In addition to re-introducing the purpose of treating carcinogenesis as the prevention of death from cancer, definitions of precision public health, precision medicine, precision oncology, and precision nutrition, and subdisciplines therein, are important to delineate. At their core, several overarching themes distinguish precision approaches in each of these disciplines from their conventional counterparts. Two of those themes are (1) that one size does not fit all, and (2) that genetic analyses and those of other omics platforms and behavioral assessment paradigms are used to predict and triage populations and individuals into plans of action that are most likely to work for them.

Precision medicine is an approach to disease treatment and prevention that considers individual variability in genes, environment, and lifestyle for each person [17]. This approach allows physicians to predict more accurately which prevention and treatment strategies for a particular disease will work in specific groups of people. It is in contrast to a one-size-fits-all approach, in which disease prevention and treatment strategies are developed for the average person (i.e., population-based health guidance), with less consideration for the differences among individuals.

Precision public health is defined as the use of data and evidence to tailor interventions to the characteristics of a single population [18]. It differs from precision medicine in terms of its focus on populations and limited use of human genomics data, although this is changing as progress is made in molecular epidemiology.

Precision oncology is defined as cancer diagnosis, prognosis, prevention and/or treatment tailored specifically to the individual patient based on the patient's genetic and/or molecular profile [19]. Exemplar approaches include targeted immunotherapy and mechanism-based therapies targeting specific cellular signaling pathways.

Oncopharmacology is the development and testing of drugs and their interactions with cancer cells [20].

Precision nutrition is an approach to developing comprehensive and dynamic nutritional recommendations based on individual variables, including genetics, microbiome, metabolic profile, health status, physical activity, dietary pattern, food environment, and socioeconomic and psychosocial characteristics [21]. In some respects, precision nutrition can be considered a subdiscipline of precision public health.

Precision onconutrition is the use of specific nutrients and dietary factors to enhance cancer treatment efficacy and to improve the prognosis for long-term survival. Precision onconutrition requires integration of an understanding of nutrient metabolism with knowledge of the signaling pathways characteristic of each molecular subtype of cancer which can be targeted to improve treatment and control efficacies [22].

Dietary oncopharmacognosy, as defined herein, identifies bioactive small molecules derived from dietary/food patterns (i.e., the collection of foods regularly consumed in a population) with cancer-relevant effects. The collection of bioactive small molecules linked to specific dietary patterns is either directly assimilated by the host during the process of food digestion or metabolized/modified by the microorganisms in the gut and thereafter exerts local and systemic effects.

3. The Top-Down Approach: Dietary Patterns

Under the backdrop that single nutrients are linked to single diseases or deficiency syndromes, e.g., vitamin C and scurvy, vitamin D and rickets, expectations were high that cancer could be prevented by a similar single nutrient paradigm as reflected by the content of one of the first comprehensive reviews of the topic in 1982 [23]. However, 50 years of investigation have generally failed to affirm these expectations [24]. In fact, the last fifteen years have witnessed an important airing of concern that diet and nutrition may not significantly impact the carcinogenic process based on the reductionist approach exemplified by single nutrient-based hypothesis testing [25][26][27][28], and in some specific cases, this approach could be harmful, e.g., vitamin A and lung cancer in smokers [29]. However, over the past decade, the single nutrient reductionist approach has been supplanted with a focus on how foods are typically consumed, i.e., dietary/food patterns, and with the analysis of cancer risk and cancer mortality when various dietary patterns are consumed [30][31][32]. This is based on the recognition that (1) individuals consume foods rather than only nutrients, (2) each food is composed of hundreds to thousands of chemicals (phytochemicals if the foods are of plant origin), many of which have bioactivity (bioactive food components), and (3) that foods eaten throughout a day can have synergistic, antagonistic, or agnostic actions that collectively may exert effects on the carcinogenic process.

The movement in the field from single nutrients to dietary/food patterns to understand the mechanistic links between diet and cancer is significant, but most studies use host systemic markers, e.g., circulating biomarkers, such as C-reactive protein for inflammation, insulin and C-peptide for insulin resistance, rather than tissue-specific markers to infer candidate mechanisms [33]. This approach may be too non-specific and lack sensitivity of the magnitude that has led to clinically effective mechanism-based small-molecule inhibitors used in cancer treatment. These well-tolerated, small-molecule pharmaceutical inhibitors that focus on specific dysregulated cellular targets have shown success with limited or no effects on host systemic biomarkers [34][35][36]. Yet, a food-derived bioactive-small-molecule approach to cancer prevention and control is lacking. A translational (i.e., both bottom-up and top-down) approach coupled with an understanding of food from a natural products/drug development perspective has the potential to unveil culinary medicine dietary approaches that elicit drug-like effects on target tissues for cancer prevention and control in specific populations. In making this statement, researchers are not proposing to make drugs from food molecules but rather are recommending the formulation of precision diets that have effects parallel to targeted therapies and that complement those treatment approaches when they are initiated.

4. Bottom-Up: Natural Products from Food

A simple definition of “natural product” is any molecule produced by a living organism [37]. While the data are limited, recent large meta-analyses indicate that some natural products of animal origin enhance cancer development [38]. In contrast, natural products in foods of plant origin commonly consumed in the diet have a greater propensity for inhibiting the carcinogenic process [39]. Since the focus of this narrative review is on the prevention and control of cancer, researchers will focus on foods that originate from plants, recognizing that a reduction in animal product consumption could also be protective.

Plants synthesize chemicals (therefore referred to as phytochemicals) that are structural or involved in metabolic processes such as reproduction, cellular defense, and cell signaling within a plant and among plants [40][41]. Generally, phytochemicals are categorized as either primary or secondary metabolites. Primary metabolites include carbohydrates, fats, proteins, and nucleic acids. Plant secondary metabolites can be classified into four major classes: terpenoids, phenolic compounds, alkaloids, and sulfur-containing compounds. They have low molecular weight (<1500 dalton) and are estimated to include over 10,000 distinct chemicals [40][41]. Primary metabolites are a source of macronutrients for humans, and secondary metabolites are a source of micronutrients (vitamins and minerals) and bioactive food components.

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