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Diet and supplements in cancer prevention and treatment: Clinical evidences and future perspectives

Claudio Vernieri^{a,b,*}, Federico Nichetti^a, Alessandra Raimondi^a, Sara Pusceddu^a, Marco Platania^a, Franco Berrino^c, Filippo de Braud^{a,d}^a Medical Oncology and Hematology Department, Fondazione IRCCS Istituto Nazionale Tumori, Via Venezian, 1, 20133, Milan, Italy^b Fondazione Istituto FIRC di Oncologia Molecolare (IFOM), Via Adamello 16, 20139, Milan, Italy^c Preventive and Predictive Medicine Department, Fondazione IRCCS Istituto Nazionale Tumori, Via Venezian, 1, 20133, Milan, Italy^d Università degli Studi di Milano, 20122, Milan, Italy

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ABSTRACT

In recent years, calorie-restricted dietary regimens and compounds such as vitamins, curcumin, green tea extracts and omega-3 fatty acids have attracted attention for their potential anticancer effects. While definitive conclusions cannot be drawn in this field, many patients adopt complementary antitumor therapies aiming to improve efficacy or reduce toxicity of chemotherapy, with uncertain benefits and the risk of additional toxicities or antagonistic interactions with standard therapies.

In this manuscript, we review the different levels of available evidence to suggest or discourage specific dietary changes or supplement use in the context of cancer prevention, reduction of tumor recurrences and survival prolongation in advanced cancers. Preventing or treating obesity, as well as adhering to healthy dietary patterns, should be recommended to both the general population and cancer survivors because they are convincingly associated with reduced risk of primary or second cancers and, in some cases, with reduced cancer recurrences. On the contrary, the role of specific interventions or supplements in patients with advanced malignancies is much more uncertain and actually a highly debated topic. With some exceptions, such as melatonin, the use of most complementary therapies cannot be encouraged, or should be discouraged, because of the lack of sufficient safety and efficacy data.

1. Introduction

Obesity and excess intake of high-calorie foods, saturated and *trans*-unsaturated fatty acids, sugar-containing beverages and red or processed meats, are recognized risk factors for several chronic pathologies, including type II diabetes mellitus, cardiovascular and cerebrovascular diseases (Eyre et al., 2004; Hill et al., 2009; Lichtenstein et al., 2006). The same factors have been associated in several, but not all, conducted studies with an increased risk of different tumors, while diets rich in whole grains, fruit and vegetables are considered protective (American Institute for Cancer Research and World Cancer Research Fund, 2007). Parallel to diet, dietary supplements, including vitamins, minerals, herbal-derived extracts and other molecules that are present in our body, have also attracted attention for their presumptive cancer-preventing properties, but results have been disappointing in most conducted studies (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994; Blot et al., 1993; Cauley et al., 2013; Hennekens et al., 1996; Hercberg et al., 2004; Lippman et al., 2009;

Omenn et al., 1996).

Even more debated is the possible role of specific diets or supplements in already established malignancies. Cancer survivors, as defined as subjects who have received a diagnosis of malignant tumor, form a large and heterogeneous clinical spectrum of patients that includes on the one hand subjects with limited-stage, surgically removed disease, and, on the other hand, patients with metastatic disease (2011). Approaching this heterogeneous population as a unique group is incorrect, because different tumor types and tumor stages require specific interventions with different therapeutic goals and expected results. In recent years, clinical trials investigating dietary interventions or supplements as adjuvants to standard antitumor therapies are increasing in number, stimulated by recent discoveries and pressure by the public opinion. Indeed, more and more cancer patients consider these complementary therapies as a safe way to play a more active role in the therapeutic process and to implement the efficacy of standard treatments (Richardson et al., 2000; Velicer and Ulrich, 2008). Future studies will hopefully clarify the actual efficacy of dietary interventions or

* Corresponding author at: Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Tumori, Via Venezian, 1, 20133, Milan, Italy.
E-mail address: claudio.vernieri@istitutotumori.mi.it (C. Vernieri).

supplements in reducing the risk of relapse in patients with limited-stage tumors, or in improving clinical outcomes in advanced cancers (Frenkel et al., 2013). To do so, it will be also crucial to investigate possible interactions between complementary and conventional anticancer treatments, including chemotherapy, radiotherapy or molecularly targeted therapies, because synergistic or antagonistic effects could arise from specific combinations.

2. Cancer prevention

Decades of research efforts tried to clarify the role of single nutrients, groups of nutrients and supplements in cancer development. Most of available evidence on diet derives from comprehensive meta-analyses of retrospective, case control, and prospective cohort studies. Prospective, randomized controlled trials (RCTs) are harder to perform in this context, mainly because it is difficult to guarantee and check long-term patient compliance to one specific dietary regimen (American Institute for Cancer Research and World Cancer Research Fund, 2007). On the contrary, evidence on supplements mostly derives from RCTs, because compliance for supplement intake is usually higher and more easily checked (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994; Cauley et al., 2013; Hennekens et al., 1996; Hercberg et al., 2004; Lippman et al., 2009; Omenn et al., 1996).

2.1. Overweight and obesity

Obesity has convincingly emerged as a risk factor for esophageal, pancreatic, colorectal, postmenopausal breast, kidney and endometrial cancers, and probably for liver and gallbladder tumors (American Institute for Cancer Research and World Cancer Research Fund, 2007); overall, obesity has been associated to 15–20% of all cancer deaths in U.S. patients (Calle et al., 2003). In obese subjects, increased levels of circulating blood glucose, insulin, insulin-like growth factor 1 (IGF-1) and estrogens could activate oncogenic and metabolic pathways that stimulate growth of pre-neoplastic cells (Park et al., 2014). Moreover, obesity is a common physiopathological trait of the so-called “metabolic syndrome”, characterized by abdominal fat excess, hypertension, chronic systemic inflammation, altered sugar and lipid metabolism, which is associated to increased cancer risk (Agnoli et al., 2010; Aleksandrova et al., 2011; Capasso et al., 2014; Lumeng and Saltiel, 2011; Zhang et al., 2008a,b).

Overweight and obesity usually stem from a combination of unhealthy lifestyle factors, namely excessive calorie intake, unbalanced macronutrients, and sedentary life, whose synergistic interaction can explain the epidemic spread of this condition in Western Countries. Foods associated with an increased risk of overweight and obesity include potato chips, potatoes, red and processed meats, sugar-added beverages, fruit juices, sweets, desserts, refined grains and butter; diets mainly consisting of nuts, whole grains, fruits, vegetables and yogurt have instead been associated with reduced obesity risk (Mozaffarian et al., 2011). Diets with relatively high protein content, and poor in fats and carbohydrates, can also cause weight gain on the long term (Freisling et al., 2016; Vergnaud et al., 2013). Interestingly, a recent prospective study, which was based on a single 24 h dietary recall, correlated low-protein diets with reduced cancer incidence and overall mortality in younger than 65 year old subjects (Levine et al., 2014).

Not only obesity prevention, but also its surgical treatment could be protective, because bariatric surgery has produced dramatic reduction of cancer risk, especially breast cancer, in some conducted studies (Adams et al., 2009; Christou et al., 2008; Sjostrom et al., 2009). It is currently unknown if such results can be replicated through dietary interventions, which are usually much less effective than surgery to induce fast reduction of body weight. It is also crucial to distinguish dietary regimens that promote safe and long-lasting weight loss from potentially dangerous dietary regimens, such as those with exaggerated relative protein intake (up to higher than 50% of total calorie amount),

which induce weight loss in the short-term period, but can cause rebound weight gain and could also increase cancer risk (Clifton et al., 2014; Levine et al., 2014; Santesso et al., 2012). The available scientific evidence suggests that obesity can be prevented or reversed with a chronic, moderate reduction of total calorie intake combined with a significant limitation in red and processed meats, refined grains, saturated fats, sugar, sugar-containing beverages and alcoholic drinks intake, and with the regular practice of moderate, occupational, recreational or domestic physical activity (Mozaffarian et al., 2011; Rippe and Angelopoulos, 2012; Sacks et al., 2009).

2.2. Single nutrients and dietary patterns

Excess dietary intake of certain nutrients, beverages or other chemical compounds is associated with an increased risk of specific cancers independently from obesity. In particular, positive associations have been found between global intake of alcoholic drinks and tumors of the oral cavity, esophagus, pancreas, liver and breast; red or processed meats and colorectal or gastric cancers; salt or salted foods and gastric tumors; aflatoxin and liver tumors (American Institute for Cancer Research and World Cancer Research Fund, 2007). On the contrary, fruit, vegetables and fibers have been associated with reduced risk of several cancers, including colorectal and lung cancer, and are considered as probably protective (American Institute for Cancer Research and World Cancer Research Fund, 2007).

Given the hundreds of nutrients, vitamins and minerals that are consumed with daily diet, single nutrients probably affect cancer risk only in case of disproportionately high (e.g. alcohol) or low (vitamins, folate) intake. Instead, dietary patterns, as defined as combinations, quantities and varieties of foods and beverages, could more broadly impact on cancer risk by setting a specific balance between different pro-tumor and anti-tumor compounds. The shift from a reductionist to a holistic approach that has occurred in the last decade helped to identify specific dietary patterns, including a “prudent/healthy” pattern, characterized by high fruits and vegetables intake, and a “western” pattern, characterized by high intake of red and processed meats. Interestingly, recent meta-analyses have reported significant inverse associations between healthy dietary patterns and the risk of breast, gastric, colorectal and oesophageal squamous cell carcinomas, as well as positive associations between western patterns and incidence of several cancers (Albuquerque et al., 2014; Bertuccio et al., 2013; Liu et al., 2014; Yusuf et al., 2012). The “Mediterranean dietary regimen”, in which unrefined grains, pulses, vegetables, fruit, olive oil and fish by far predominate over red and processed meats, saturated fatty acids and high-calorie foods, is one “protective” pattern often associated with lower risk of several cancer types (Agnoli et al., 2013; Buckland et al., 2013; Schwingshackl and Hoffmann, 2015). In particular, a RCT carried out in Spain to test the effect of Mediterranean diet supplemented with extra-virgin olive oil on the incidence of cardiovascular events (de Lorgeril et al., 1998; Toledo et al., 2015) suggested a strong protective effect also against the occurrence of postmenopausal breast cancer. In particular, the huge consumption of olive oil (over 20% of total calories) in the experimental group suggests that the intake of monounsaturated fats can be protective (Berrino, 2016). The role of different fats, namely saturated, trans-unsaturated, monounsaturated, w-6 and w-3 polyunsaturated ones, on cancer risk has long been investigated. Coherent with preclinical studies, the available evidence supports the hypothesis that high saturated fat content and high dietary w-6:w-3 polyunsaturated fatty acid ratio are associated with increased breast and colorectal cancer risk (Murff et al., 2009; Murff et al., 2011; Sczaniecka et al., 2012; Sieri et al., 2014). However, results on polyunsaturated fatty acids are not univocal (Azrad et al., 2013;).

2.3. Supplements

Based on retrospective studies suggesting a chemo-preventive role

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