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Perspective

Gender-Dependent Metabolism of Flavonoids as a Possible Determinant of Cancer Risk

Katrin Sak* and Hele Everaus
Department of Hematology and Oncology, University of Tartu, Estonia

***Corresponding author:** Katrin Sak, Department of Hematology and Oncology, University of Tartu, L. Puusepa 8, 51014 Tartu, Estonia

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Editorial

Numerous studies have demonstrated that malignancies develop more commonly in men than in women and also the prognosis of cancer is generally worse in males than in females, revealing lower overall survival and higher mortality rates [1-3]. This well-established difference is not unique to a particular population occurring consistently across the world [1,2]. However, the reasons behind this gender disparity have still remained rather unclear. Although this feature can be attributed to some extent to the hormonal differences, the disparity in cancer incidence between males and females appears already in early childhood when hormonal differences have still not expressed [1]. Therefore, some other determinants explaining the higher tumor susceptibility of males must evidently exist. These factors probably include behavioral aspects, environmental and occupational exposures, immune surveillance, differences in antioxidative capacity and metal toxicity, but also certain genetic factors [1,2]. It is even possible that some of these differences may come from various prenatal exposures [1]. As the endogenous causes for higher incidence of malignancies in males are largely unknown, we suggest in this short perspective one more factor that potentially could contribute to the gender disparity in cancer susceptibility, i.e. differences in the metabolism of chemopreventive food components and in anticarcinogenic properties of the respective metabolites.

Today, it is widely accepted that dietary flavonoids, including for instance commonly occurring flavonols quercetin and kaempferol, flavones apigenin and luteolin, green tea catechins, and isoflavone genistein, have strong anticancer potential exerting antiproliferative, cytotoxic, proapoptotic, antiinflammatory, antiangiogenic, antimetastatic, and antiinvasive activities [4]. These plant secondary metabolites are polyphenolic compounds that were originally proposed to be required for humans as vitamins, termed as "vitamins P" [5]. Although this statement was refuted later on, the strong potential of plant pigments in the fighting against cancer has proven in numerous experimental studies both *in vitro* cell cultures as well as in animal (rodent) models [6,7]. Moreover, several epidemiological studies have demonstrated that regular intake of dietary sources rich in flavonoids, i.e. fruits and vegetables, nuts, spices, and medicinal herbs, is correlated with the reduced risk of development of malignant disorders [8-10]. It is even stated that people who daily eat approximately five servings of vegetables and fruits have about 50% reduced risk of developing cancer [8].

To date, more than 6000 structurally different flavonoids have been described in nature being widely distributed in plant origin foods and possessing a vast potential for mammalian defense against different chronic diseases, such as malignancies. However, application of anticancer properties of flavonoids in pharmaceutical field and clinical settings is still hindered by their poor bioavailability that is defined as the fraction of administered bioactive compound entering the systemic circulation in unchanged form, i.e. without structural modifications [10]. Indeed, the plasma concentrations of parent flavonoids in humans are very low and significantly below the doses needful for therapeutic effects; or in other words, pharmacologically effective concentrations of these phytopigments are mostly not achievable through the dietary consumption [6,8,11-13]. For instance, the baseline plasma concentrations of flavonol quercetin from dietary sources are about 50-80 nM remaining considerably lower than the cytotoxically active doses [14-16]. Similarly, the peak plasma concentration of green tea flavanol epigallocatechin gallate (EGCG) is only about 150 nM after drinking two cups of green tea being certainly not sufficient for exerting anticancer activities [14,17]. The major drawbacks for such a low oral bioavailability of flavonoids include limited water solubility and stability, poor absorption across gastrointestinal epithelial cells, and extensive and rapid metabolic bioconversion of these plant-derived edible agents in the small intestine and liver, mainly via glucuronidation and/or sulfation conjugations [9]. Moreover, there are several evidences demonstrating that bioavailability of flavonoids depends also on the host related factors, including gender and age/maturity of the individual subjects [12]. In this way, the capacity of liver metabolism of flavonoids has been reported to be determined by the gender of rats [9]. Indeed, studies on the metabolism of flavone apigenin in Wistar rats revealed clear differences between male and female animals with regard to the proportion of glucuronidated and sulfated derivatives eliminated via urinary route, probably explained by the gender-specific regulation of certain phase I and II metabolic enzymes [18]. Similarly, gender was shown to significantly affect also the sulfation of monohydroxyflavones in rat and mouse liver S9 fractions [19]. However, gender differences in bioconversion of flavonoids have still drawn only little attention so far and certainly need further investigation and experimental evidences both relating to the nature and anticancer properties of circulating metabolites. It is evident that actual physiological responses are mediated by the enzymatic products reaching to bloodstream rather than the respective parent flavonoids. At that, it is also important to bear in mind that results obtained with animals (rodents) may not be directly extrapolated to humans [19,20]. Therefore, much work is needed to be accomplished in the issue of gender-dependent metabolism of flavonoids in humans as well as the changes in anticancer efficacy of metabolites formed during such bioconversion. Also, the gender-specific genetic

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polymorphisms in drug-metabolizing enzymes are definitely worth of thorough studies and should be focus of immediate future research.

At present, reports can be found about the inverse association of flavonoid-rich food intake with systolic blood pressure in women but not in men, showing that high consumption of polyphenols-containing plant foods may be beneficial for prevention of cardiovascular diseases in women [21]. Also, greater intake of various subclasses of dietary flavonoids, such as flavanols, flavonols, flavones and flavanones, has been related to the higher bone mineral density among women but not among men [22]. To the best knowledge of the authors, there are no such data available concerning the possible impact of gender upon the effect of flavonoid-rich food consumption on cancer risk and overall survival rate; however, if the nature and proportion of circulating metabolites differ between male and female subjects it is probable that also the cytotoxic potential of these derivatives could vary. These studies with possible insight to the respective molecular mechanisms are definitely of great future interest. In any case, it is clear that to realize the maximum of biological potential of natural polyphenolic agents for both men and women, the oral bioavailability of parent flavonoids with established anticancer bioactivities must be improved by using novel scientific and technological strategies, including chemical modifications and/or nanotechnological approaches.

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