

# The Global Fruit & Veg Newsletter



n° 8

March  
2016

## POLYPHENOLS

### Edito

Polyphenols are widely consumed with fruits, vegetables and plant-derived beverages such as fruit juices, tea, coffee or wine. They form one of the most extensively studied families of food bioactives, with quite diverse biological properties including antioxidant, anti-inflammatory, antimutagenic, antiproliferating, or antiangiogenic effects, widely documented in preclinical studies. Many randomized clinical trials published over the last 10-15 years have shown some beneficial effects of polyphenols or polyphenol-rich foods on surrogate markers of cardiovascular diseases and diabetes, and on cognitive functions, providing a growing body of evidence to substantiate their protective role in the prevention of major chronic diseases and of functional declines associated to ageing.

In this issue, three papers discuss the role of polyphenols in the primary prevention or recurrence of colorectal cancer and in the reduction of total mortality, as studied in the EPIC and inCHIANTI cohorts. All authors stress the limits of current epidemiological evidence to support a protective role of polyphenols against colorectal cancer and other diseases and the need for more prospective studies with improved methodologies for measuring exposures to over 500 polyphenols scattered in a large diversity of foods. Such studies should contribute to the development of evidence-based recommendations for the general population or for specific groups of the population at risk of developing particular diseases.

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**July/August 2009** : T. Lobstein; J. Utter; IK. Crombie; DJ Barr-Anderson (Close environment impact on F&V consumption)  
**September 2009**: C. Rowley; IC. Figueiredo, CA. Monteiro; C. Pollard; HM. Black (F&V in the world)  
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# Dietary polyphenol intake in Europe

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## Daily polyphenol intake across European countries

Diets high in fruits and vegetables are widely recommended for their health-promoting properties. Fruits and vegetables are rich in polyphenols, which have been extensively studied due to their antioxidant, anti-inflammatory and anti-carcinogenic properties. However, epidemiologic evidence for the impact of dietary polyphenols on the risk of chronic diseases is still limited<sup>1</sup>.

The dietary intake of individual polyphenols has been estimated in a small number of studies, particularly in Europe<sup>2</sup>. Phenol-Explorer<sup>3</sup>, the only food composition database containing food composition data on all known individual polyphenols, and standardized dietary questionnaires allowed to compare intake of all polyphenols across countries in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, where data on 10 European countries was pooled together. A wide range of total polyphenol intake values and a south-to-north geographical gradient among EPIC centers is observed, with highest values found in non-Mediterranean countries (1284mg/d) and lowest in Mediterranean countries (1011mg/d). Highest intake is noted in Danish men (1786 mg/d) and the lowest intake in Greek women (584 mg/d)<sup>2</sup>.

## What are the major polyphenol classes consumed?

The main polyphenol contributors are phenolic acids in non-Mediterranean countries (~55%) and flavonoids in Mediterranean countries (~49%). In the UK, flavonoids account for approximately 60% of total polyphenols. The contribution of other polyphenol classes such as stilbenes, lignans, alkylresorcinols or tyrosols is in total less important (<7%)<sup>2</sup>.

## What are the main individual polyphenols consumed?

The Phenol-Explorer database contains food content values for 502 polyphenols, of which 437 are consumed in Europe, including 94 consumed at a level >1mg/d<sup>2</sup>. The most widely consumed polyphenols are for phenolic acids, the caffeoylquinic and feruloyl quinic acids; and for flavonoids, proanthocyanidins and hesperetin. It is very relevant to study individual polyphenols, since they may have different bioavailability and biological effects.

## What about the main food sources of polyphenols?

Polyphenols are exclusively present in plant-based foods. Coffee, tea, and fruits are the most important food sources of polyphenols, although depending on the country their relative contribution can be quite different. Coffee is the main source of polyphenols in both non-Mediterranean and Mediterranean countries (41% and 36%, respectively) and the major source of phenolic acids everywhere (75%). Tea is the most consumed source of polyphenols in the UK (40%), being the main source of flavonoids in the UK (64%) and non-Mediterranean countries (34%), but not in Mediterranean countries (9%). Fruits and fruit juices are the most abundant source of flavonoids (48%) and the second of total polyphenols (26%) in Mediterranean countries. Vegetables are in comparison minor contributors of polyphenol intake (<5%), because concentration of polyphenols is usually lower in vegetables than in fruits and substantial amounts of polyphenols are also lost during cooking (25 to 75%)<sup>4</sup>. Wine, especially red wine, is also a primary source of polyphenols (10% of total polyphenols, mainly flavonoids) in Mediterranean countries. It is also the main source of resveratrol<sup>2</sup>.

## Determinants of polyphenol intake

The intake of flavonoids is higher in women, older subjects with a BMI<25, non-tobacco consumers with a high educational level and physically active. Therefore, the intake of flavonoids tends to be associated with healthy lifestyle habits. In contrast, intake of phenolic acids is higher in younger men with a BMI≥30, and especially in smokers drinking more coffee<sup>2</sup>.



## Summary and what is next?

There is a large variability in the nature and amount of polyphenols consumed in Europe, with a total intake ranging from 500 to 2000 mg/d and individual preference for coffee, tea and fruits largely explain these variations<sup>2</sup>. Flavonoids have been the most widely investigated polyphenol class. However more attention should also be paid to phenolic acids which also contribute to a major fraction of polyphenol intake. An accurate and comprehensive estimation of polyphenol intake will be very valuable for future research on the role of polyphenols in the prevention of chronic diseases such as diabetes, cardiovascular diseases and cancer. Further investigation in the validation of polyphenol intake using biomarkers is also needed<sup>1</sup>.

## References

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# Evidence for a protective effect of polyphenol-rich diet intake on healthy aging from the InCHIANTI study

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## Diet strategy for slowing effects of aging

The number of people aged 65 years and older is projected to increase from 18% in 2014 to 29% in 2080. The continuing population aging is a challenge for public health policies, since it is desired that this increase in life expectancy does not occur at expenses of lower quality of life. Thus, it is necessary to increase research on the benefits of healthy eating habits in order to identify the best dietary recommendations. These will enable the prevention or delay of symptoms, syndromes and diseases associated with aging, such as frailty, physical and cognitive decline. Amongst existing dietary patterns, diets high in fruits and vegetables have been shown protective effects against cardiovascular and neurodegenerative diseases, cancer and total mortality. Fruits and vegetables are rich, among other potentially beneficial compounds, in phytochemicals, such as polyphenols. Polyphenols constitute a very heterogeneous group, with over 500 different compounds. The number of experimental studies on the protective role of polyphenols in aging has grown exponentially during the last years, even though the epidemiological evidence is still limited. Furthermore, associations observed between polyphenols and health are compromised because the use of self-reported questionnaires, which may be subject to both systematic and random measurement errors. As a result, nutritional biomarkers are being highly used in nutrition research, because they provide a more accurate and objective measure to estimate the dietary polyphenol exposure.

## Polyphenols and aging: epidemiological evidence from the InCHIANTI study

Recently, we investigated the associations between dietary polyphenols exposure, using dietary questionnaires and biomarkers, and cognitive and physical decline, frailty and total mortality among the participants aged 65 years or more within the InCHIANTI cohort. The InCHIANTI is a prospective population-based study conducted in two municipalities (Bagno a Ripoli and Greve in Chianti) adjacent to the city of Florence (Italy). It was designed to evaluate risk factors affecting the loss of mobility in the older population. The dietary intake of total polyphenols and resveratrol was estimated

using a validated food frequency questionnaire and an *ad hoc* database of food composition on polyphenols, created from the two only databases available in the literature: USDA and Phenol-Explorer databases. The urinary concentration of total polyphenols and resveratrol metabolites was determined by Folin-Ciocalteu colorimetric and mass spectrometry methods, respectively. We observed that participants in the highest tertile of total urinary polyphenols had a (47, 60, 64 and 30 %) reduction in the risk of global cognitive and physical decline, frailty and total mortality, in comparison with those in the lowest tertile. However, no association with total dietary polyphenols was observed. In these studies, we demonstrate the importance of assessing dietary polyphenol exposure whenever possible, using biomarkers and not only using dietary questionnaires. Additionally, habitual dietary exposure of resveratrol was associated with a lower risk of developing frailty over a three years follow-up combining of both measures (diet and biomarker) as well as individually.

The potential underlying mechanism of action of polyphenols may be due to their antioxidant and anti-inflammatory activities. For example, polyphenols reduce neuronal damage and death from oxidative reactions by inhibiting the generation of reactive oxygen species, lipid peroxidation, protein oxidation, metal chelation, neuronal apoptosis, and damage to cellular signaling.

## Recommendations and future research plans

The message that we can extract for the general population, so far, could be the recommendation of an intake above 600 mg/d of polyphenols within a healthy dietary pattern, rich in fruits and vegetables. This amount can be achieved by eating 5-6 servings of polyphenol-rich foods per day, such as fruits, vegetables, wine, nuts, chocolate, coffee or tea.

Future clinical and epidemiological studies are warranted to replicate these associations, especially using biomarkers, in other populations. The advances in polyphenols research will be important to make dietary recommendations for developing effective public health policies and for improving the autonomy and quality of life of older people.



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Based on :

Rabassa M., Cherubini A., Zamora-Ros R., Urpi-Sarda M., Bandinelli S., Ferrucci L., Andres-Lacueva C. Low levels of a urinary biomarker of dietary polyphenol are associated with substantial cognitive decline over a 3-year period in older adults: The invecchiare in CHIANTI study. *J. Am. Geriatr. Soc.* 2015;63:938-946. doi: 10.1111/jgs.13379.



# Polyphenols, inflammation and colorectal cancer

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The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report highlights clear associations between red and processed-meat intake, higher alcohol intake and higher colorectal cancer risk. Meanwhile, dietary fibre intake is associated with a lower risk. The evidence is less clear for milk and calcium, non-starch vegetables, fruit and fish. There has been, however, increased interest in the role of bioactive compounds found in plant foods, and the role they play in health.

Population studies have shown that habitual consumption of diets rich in plant foods (fruit, vegetables, and plant beverages such as tea or coffee) was linked to a lower risk of several chronic diseases including cancer. Plant foods contribute toward health via their amino acids, polyunsaturated fatty acids, vitamins, minerals, and dietary fibre, but also via a range of bioactive compounds, known as polyphenols. These polyphenols are ubiquitous in plant foods, and include flavonoids, flavonols, flavanones, phenolic acids, to name a few.

Colorectal cancer (CRC) is the 2<sup>nd</sup> most common cause of cancer-related death in the UK (2010), the third most common cancer throughout the world, and the fourth most common cause of death. There is still a limited understanding of how CRC occurs. However, both genetic and environmental factors are associated with an increased risk of CRC. With only 5-10% of CRC occurring in patients with familial history of the disease, most cases are “sporadic”, following spontaneous mutations. These cases of sporadic CRC are mostly associated with lifestyle factors, including the diet.

## Inflammation

Inflammation is an important “hallmark” of cancer and has a role in the progression of CRC.

In a vicious cycle, inflammation promotes tumour development, which in turn generates further inflammation. Slowing down the inflammation “fire” is a key strategy in managing the disease. Anti-inflammatory molecules can achieve this, however, they can also be toxic in high doses.

Polyphenols are part of the diet, therefore their toxicity is low, in the doses usually ingested in foods. A key feature of polyphenols as “bioactives” is their anti-inflammatory properties. However, this has mostly been demonstrated in *in vitro* experiments, using human or animal cells. Therefore caution must be applied when interpreting the results of these studies. With focus mostly on “pure” compounds or “extracts”, tested in high dose, there is evidence that green tea extract enriched with catechin and epigallocatechin gallate (EGCG), genistein, quercetin, kaempferol, curcumin and resveratrol, may modulate some of the key inflammatory pathways (including, for example, COX-2, NF- $\kappa$ B).

The bioavailability of polyphenols is poor, which means that they do not get easily absorbed and made available to the organs. They instead remain inside the gut, where they are metabolised by the microbiota. It is where they may be most potent. In animal models of inflammatory bowel disease, polyphenols administration successfully decreased inflammation. The evidence in humans is, however, not as convincing.

## Cohort studies

The EPIC study (> 500,000 adults from ten European countries) showed a 40% reduced risk of CRC in those with the highest intake of fibre and fruit and vegetable. Population studies have been carried out

around the globe, with focus on the association between polyphenol, flavonoid or phenolic-rich diets and the risk of CRC. The results are conflicting, with some studies finding negative associations between specific classes of polyphenols and CRC (in Italy, 36% reduction risk with increased intake of isoflavones, anthocyanidins, flavones, and flavonols but not flavan-3-ols, flavanones, or total flavonoids; in Spain, 41% CRC risk reduction with increased intake of total flavonoids, flavones, flavanols, procyanidins, and lignans but not anthocyanidins, flavanones, flavonols, flavan-3-ols, or isoflavones). Other groups found no associations between CRC and polyphenol intakes, but evidence of reduction in colon cancer risk instead (including Scotland and US studies). The reasons for these conflicting results are many, and may include differences in patient dietary data collection (tools and methods), and confounding factors not consistently considered (age, activity level, smoking, alcohol consumption). Some studies may also have been too small to be able to show an association between polyphenols and CRC. Based on these studies, it is not possible to conclude that polyphenol intake is inversely related to CRC risk. The reduction of CRC could also be due to fibre, vitamins, and other bioactives present in fruit and vegetables.

## Trials and interventions

There are very few trials or interventions in human subjects to test the hypothesis that polyphenols may be important in the management of CRC (possibly via anti-inflammatory action). Such trials are essential to establish a causal link between the dietary bioactives and disease protection. A trial in the US relied on dietary recommendations to increase polyphenols intake, with a view to study polyp recurrence, showed a 76% decrease in the risk of recurrence in those with a higher flavonols intake.

In another study, authors concluded that treatment with flavonoids could reduce the recurrence rate of neoplasia in those with resected colon cancer because the recurrence rate after resection was, after 4 years, 7% in the treated group compared to 47% in the control group.

There are not enough trials available to draw a conclusion on the protective effect of polyphenols against CRC. Studies in other patient groups, where inflammation is a key disease contributor, are promising: a 6-month placebo-controlled trial of curcumin in patients with ulcerative colitis led to a decreased relapse rate in the treatment group (5%) versus placebo-control group (21%).

## Recommendations

There is no reference for dietary intake of polyphenols. Recommendation of a diet rich in fruit and vegetables will provide a high amount of polyphenols. The evidence from population and intervention studies is not sufficient to draw a conclusion and prescribe polyphenols with a view to prevent or treat CRC. It is however safe to increase plant foods to increase polyphenols consumption, and this, combined with weight management, limiting alcohol and cigarettes and increasing physical activity, is the recommended approach to reduce CRC risk.

Further research may yield results supporting new recommendations, especially for those at increased risk, to complement the bowel screening programme. To achieve this, there is a need for well-designed studies, using the correct doses of bioactives, in the most appropriate dose and matrix (or “form”), in large numbers of patients whose diets will be closely monitored. Such study design is challenging, but nonetheless required to draw firm conclusions.

### To know more

“Little, C. H., Combet, E., McMillan, D. C., Horgan, P. G., & Roxburgh, C. S. D. (2015). The Role of Dietary Polyphenols in the Moderation of the Inflammatory Response in Early Stage Colorectal Cancer. *Critical reviews in food science and nutrition* DOI:10.1080/10408398.2014.997866”