Archives of Biochemistry and Biophysics 501 (2010) 170–175

Contents lists available at ScienceDirect

Archives of Biochemistry and Biophysics

journal homepage: www.elsevier.com/locate/yabbi

Review

Phytoestrogen consumption and association with breast, prostate and colorectal cancer in EPIC Norfolk

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ARTICLE INFO

Article history:
Received 25 January 2010
and in revised form 1 May 2010
Available online 1 June 2010

Keywords:
Phytoestrogens
Isoflavones
Lignans
Enterolignans
Equol
Food composition
Breast cancer
Prostate cancer
Colorectal cancer

ABSTRACT

Phytoestrogens are polyphenolic secondary plant metabolites that have structural and functional similarities to 17β-oestradiol and have been associated with a protective effect against hormone-related cancers. Most foods in the UK only contain small amounts of phytoestrogens (median content 21 μg/100 g) and the highest content is found in soya and soya-containing foods. The highest phytoestrogen content in commonly consumed foods is found in breads (average content 450 μg/100 g), the main source of isoflavones in the UK diet. The phytoestrogen consumption in cases and controls was considerably lower than in Asian countries. No significant associations between phytoestrogen intake and breast cancer risk in a nested case-control study in EPIC Norfolk were found. Conversely, colorectal cancer risk was inversely associated with enterolignan intake in women but not in men. Prostate cancer risk was positively associated with enterolignan intake, however this association became non-significant when adjusting for dairy intake, suggesting that enterolignans can act as a surrogate marker for dairy or calcium intake.

Introduction

Phytoestrogens are a group of non-steroidal polyphenolic plant metabolites that induce biological responses and can mimic or modulate the action of endogenous oestrogens, often by binding to oestrogen receptors [1]. In animals, adverse effects of phytoestrogen-rich fodder such as infertility and hyper-oestrogenisation have first been described in the 1940s as ‘‘clover-disease” in sheep grazing on clover-rich pastures [2]. Subsequently, the adverse effects of oestrogenic plant compounds have also been described in cattle [3–5], Guinea pigs [3,6], rabbits [7], mice [8] and cheetahs [9]. Despite these adverse effects in animals, similar effects have not been observed in humans on a phytoestrogen-rich diet [10].

The bioactivity of phytoestrogens is based on their structural similarity with 17β-oestradiol [11–14] and their ability to bind to oestrogen receptors [15]. An aromatic ring and a hydroxyl-group are important features for a compound to bind to the receptor [16] and the structure of phytoestrogens with a *p*-hydroxy-substituted aromatic ring, 1.2 nm (12 Å) away from a second planar hydroxyl-group, resembles the structure of oestradiol [17]. However, whereas oestradiol has a similar affinity for the oestrogen α and β receptor (ERα and ERβ), there are marked differences for phytoestrogens. For example, the isoflavone genistein exhibits an up to 30-fold greater affinity for ERβ [18] and coumarins were shown to have a five-times higher relative binding affinity to ERβ [19]. Therefore, phytoestrogens may cause some of their clinical effects by selectively triggering ERβ mediated responses [18]. Compared with oestradiol, phytoestrogens have only a weak oestrogenic activity (10^{-2} to 10^{-3} compared with 17β-oestradiol) but can compete with oestradiol at the receptor complex; however, they fail to stimulate a full oestrogenic response [20–25]. Apart from their effect on oestrogen receptors, phytoestrogens can also act as inhibitors of enzymes such as tyrosine kinase [26] and DNA toposiomerase [27]. It is however mainly their anti-oestrogenic activity which raises the possibility that they are protective in hormone-related diseases [28], in particular breast, colorectal or prostate cancer. Epidemiological studies conducted so far however have failed to show such an effect conclusively, in particular in populations with low habitual phytoestrogen consumption such as in Europe or the US. A meta-analysis of eight studies conducted in high soya-consuming Asians showed a protective effect of soya isoflavones against breast cancer, studies conducted in Europe [29] [30,31] or the US [32] failed to find a significant effect. Likewise, of eight studies included in a meta-analysis to investigate associations between isoflavone intake and the risk for prostate cancer only those with the highest intake showed a significant (inverse) association [33].

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doi:10.1016/j.abb.2010.05.018

Phytoestrogen consumption

The main sources of dietary phytoestrogens are fruits and vegetables, but they are also present in dairy products [34,35] and in other foods of animal origin [36]. The principal classes of phytoestrogens are isoflavones (found mainly in legumes, chick-peas and soybean), prenylated flavonoids (present in hops), coumestans (found in young sprouting legumes like clover or alfalfa sprouts) and lignans (found in cereals, linseed and other fruits and vegetables). In plants, phytoestrogens occur predominantly as glucosides which – upon consumption – are hydrolysed by intestinal glucosidases to release aglycones [37]. These aglycones can then be further metabolised by the intestinal microflora; isoflavones to metabolites like equol and O-desmethylangolensin, [34,38]; lignans to enterolactone and enterodiol [39].

Phytoestrogen exposure can be determined using two different methods: either directly by measuring diet or indirectly by using biomarkers in plasma or urine [40]. Biomarkers are considered to be more reliable due to limitations in dietary assessment [41], but their application is often not feasible, in particular in larger studies or to assess exposure in the general population. Furthermore, the measurement of urinary or serum biomarker is often affected by inter-individual differences in metabolism as most analytical methods used for biomarker measurement only determine the most common metabolites (Fig. 1). For this reason, accurate information on the phytoestrogen content of foods commonly consumed is crucial and several studies have been conducted so far (Table 1).

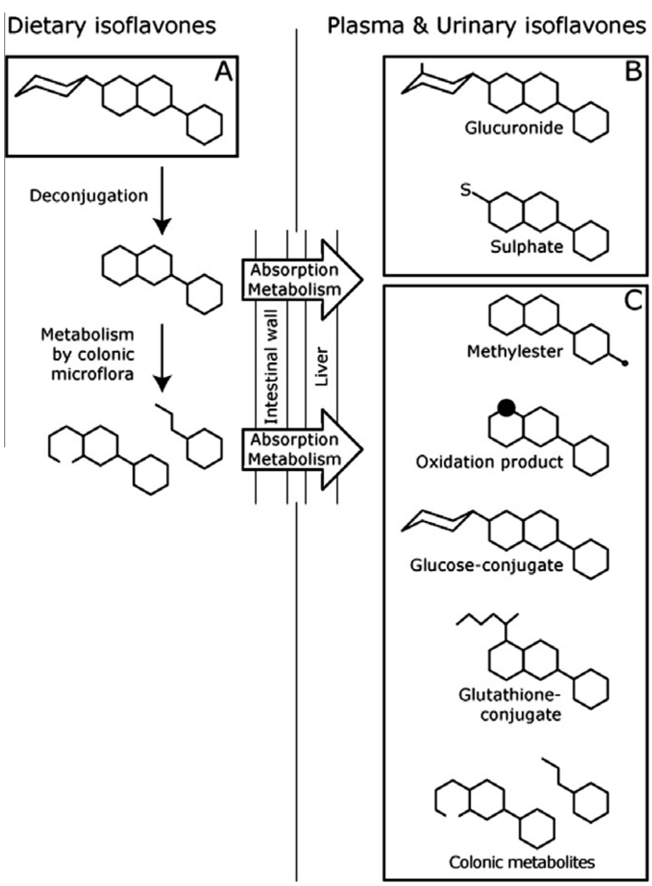

Fig. 1. Assessment of phytoestrogen exposure by biomarker. Dietary phytoestrogens (A) undergo extensive metabolism both by the gastro-intestinal microflora and upon uptake in the human body. However, most analytical methods for biomarker measurements only determine the most common metabolites (e.g. B) whereas other metabolites (C) remain undetected. Inter-individual difference in metabolism will therefore affect the apparent biomarker concentration and can therefore introduce larger variability and lead to underestimation of exposure.

Phytoestrogen content of UK food

We have recently developed the most comprehensive database of phytoestrogen content in UK food [36,42–44], covering more than 500 items. The majority of foods consumed in the UK has a phytoestrogen content of less than 100 μg per 100 g wet weight, indeed the median content is 21 μg/100 g. The highest phytoestrogen content was found in soya and soya-containing foods, such as for example soya flour (125 mg/100 g), soya infant formula (19 mg/100 g), soya beans (18 mg/100 g) or soya milk (9 mg/100 g). The highest amount of phytoestrogens in non-soya-containing foods was found in linseeds (19 mg/100 g). Lignans were the main type of phytoestrogens found in most foods, with the exception of foods from *Fabaceae* which contained mainly isoflavones, in particular daidzein, genistein and glycitein. High levels of biochanin A (400 μg/100 g) were only found in chick-peas and chick-pea based foods.

Despite knowledge of the presence of phytoestrogens in foods of animal origin for some time – in particular in milk [34–36] – very little data about the phytoestrogen content are available. We have conducted the first comprehensive analysis and found phytoestrogens in milk and dairy products, eggs, meat, fish and seafood [36], although the amount in some foods, in particular fish and seafood (2–9 μg/100 g), was very low. Whereas in meat, fish and seafood virtually all phytoestrogens are directly plant-derived, a major proportion of the phytoestrogens found in eggs and dairy products were derived from gastro-intestinal metabolism of plant precursors. The phytoestrogen content in milk and other dairy products depends on a variety of factors such as fodder and season and vary between different countries, for example: Australia (5–29 μg/100 ml equol) [45], France (1–29 μg/100 ml equol, 1–9 μg/100 ml enterolactone) [46], Finland (6 μg/100 ml) [47] and the United Kingdom (1–8 μg/100 ml equol, 3–9 μg/100 ml enterolactone) [36].

The phytoestrogen content in eggs was lower than in milk products and most phytoestrogens (mainly isoflavones) were found in the yolk. In contrast to milk-based products, the amount of equol was higher than the amount of enterolignans present. Although the isoflavones content was highest in eggs from hens kept in barns, there was no statistically significant difference between different types of chicken husbandry.

The phytoestrogen content of some foods commonly consumed in the UK is shown in Table 2. Most foods contain only small amounts and the main type of phytoestrogens are lignans. The highest amount of phytoestrogens in commonly consumed foods in the UK is found in bread where up to 1 mg/100 g were found in non-speciality breads (mean content 450 μg/100 g), although the phytoestrogen content of flour is only 20–40 μg/100 g. The main type of phytoestrogens in bread are isoflavones and they are derived from soya which is added to the dough as part of the *Chorleywood Bread Process* (CBP)[1] [48] to help improve the bread quality; for this reason, bread is one of the main sources of phytoestrogens in the UK diet [49]. In countries where bread is prepared using different processes, the phytoestrogen content is considerably lower, for example 190 μg/100 g for commercial white bread in the US [50].

Phytoestrogens and cancer risk in EPIC Norfolk

The updated food-composition database allowed a more accurate exploration of associations between dietary phytoestrogens and the risk for breast, colorectal and prostate cancer in a nested case-control study in EPIC Norfolk [31]. 25,639 participants

[1] *Abbreviations used:* CBP, Chorleywood Bread Process; SHBG, sex-hormone binding globulin.