

CURRENT EPIDEMIOLOGICAL KNOWLEDGE ABOUT THE ROLE OF FLAVONOIDS IN PROSTATE CARCINOGENESIS

K. Sak*

NGO Praeventio, Näituse 22–3, Tartu 50407, Estonia

Numerous experimental studies have demonstrated anticancer action of polyphenolic plant metabolites. However, data about associations between dietary intake of plant-derived flavonoids and prostate cancer risk are still sparse and inconsistent. This mini-review compiles the epidemiological findings published to date on the role of flavonoids in prostate tumorigenesis, discusses the reasons of inconsistencies and elicits the promising results for chemoprevention of this malignancy. Long-term consumption of high doses of soy isoflavones can be the reason of markedly lower clinically detectable prostate cancer incidence among Asian men compared to their counterparts in the Western world. The ability to metabolize daidzein to equol, the most biologically active isoflavone, by the certain intestinal bacteria also seems to contribute to this important health benefit. The increasing incidence rate of prostate cancer related to adoption of westernized lifestyle and dietary habits makes the issue of chemoprevention ever more important and directs the eyes to specific food components in the Eastern diet. If further large-scale epidemiological studies will confirm the protective effects of isoflavones against prostate cancer, this could provide an important way for prostate cancer prevention, as diet is a potentially modifiable factor in our behavioral pattern.

Key Words: chemoprevention, epidemiological findings, flavonoids, plant metabolites, prostate cancer.

The incidence rate of clinically detectable prostate cancer is historically markedly lower in Asian countries, such as Japan, China, India, Singapore or Korea, compared to the Western world, including men living in American, European countries or Canada [1–9]. This age-adjusted difference between Asian and Western populations can reach even 10- to 90-fold [10–12]. However, in parallel to adoption of westernized habits among Japanese men, the incidence rate of prostate tumors is gradually rising [1, 6, 7, 9]. Also, Japanese migrants to the United States as well as foreign-born Asian Americans reveal an increased incidence of prostate neoplasms [3, 6, 10, 11, 13–16]. On the contrary, the incidence of clinically undetectable or latent prostate cancers in autopsy studies is rather similar between men from Asian and American countries, suggesting that some components in the Asian diet can block progression of latent cancers to the more advanced form [3, 6, 8, 14]. Therefore, the etiology of prostate tumor might involve environmental factors, such as dietary habits, which can play a major role in the pathogenesis of this malignancy [1, 3–6, 11–20]. A traditional Asian diet is rich in soy-derived phytoestrogens or isoflavones that have been related to the lower incidence of prostate cancer in this region [3, 7–9, 14, 21].

Plant-based food items contain various phytochemicals, including flavonoids, with anticarcinogenic properties [18]. These polyphenolic compounds may influence prostate tumorigenesis through multiple different mechanisms; flavonoids have been shown to exhibit antioxidant, antiinflammatory, antiproliferative, proapoptotic, antiangiogenic and antimetastatic activities [13, 18, 22]. Although numerous experimental cell culture and animal studies have demonstrated different effects of these plant metabolites against prostate cancer, findings from epidemiological studies

are still limited and far from definite [6, 12, 16, 19, 21, 23–26]. To comprehend the current state of epidemiological evidence on the role of various flavonoids on prostate tumorigenesis, the findings published to date about associations between dietary intake of flavonoids and the risk of prostate cancer were compiled and are analyzed in this minireview. In addition, the blood and urinary biomarker data are included in the survey. These data are presented in Tables 1–3. Also, the potential factors for inconsistencies are put forward and discussed.

EPIDEMIOLOGICAL DATA ABOUT THE ROLE OF FLAVONOIDS ON PROSTATE CANCER RISK

Case-control studies

No statistically significant associations with the risk of prostate cancer were found for total flavonoids or flavonoid subclasses, including flavones, flavonols, flavanones, flavanols, isoflavones and anthocyanidins in Italian population, showing no protective effects of flavonoids against prostate tumorigenesis [21]. These results were in general agreement with two other case-control studies, revealing no significant relationships between intake of flavones (apigenin, luteolin) and flavonols (kaempferol, myricetin) and prostate cancer incidence among American men [18, 27]. However, a suggestive inverse association was still reported for flavonol quercetin with a 36% decrease in prostate cancer risk for men in the highest quartile of quercetin consumption compared to those in the lowest quartile of intake [18].

Similarly to the work with Italian men, no overall relationships between consumption of total or individual isoflavones (genistein, daidzein) and prostate cancer risk were observed also in Swedish [17, 28], Scottish [5], or English population [12, 29]. However, these results are different from the findings of case-control studies conducted with Japanese [1] and Chinese men [15], which observed a protective effect of intake

Table 1. Epidemiological case-control studies on dietary intake of flavonoids and prostate cancer risk

Flavonoid subclass	Certain compound	Study ^a	Population	Controls ^b	Cases/controls	Intake comparison (low vs high, mg/day) ^c	Multivariate-adjusted OR/RR ^d	p for trend ^e	Age, years	Reference
Flavonoids			Italian	HB	1294/1451	(Q5)	1.20 (0.92–1.58)	0.44	46–74	[21]
Flavones			Italian	HB	1294/1451	(Q5)	1.09 (0.85–1.40)	0.88	46–74	[21]
Flavones	Apigenin		American	HB	83/107		0.83 (0.45–1.51)	0.54		[27]
Flavones	Luteolin		American	HB	83/107		0.83 (0.45–1.51)	0.54		[27]
Flavonols			Italian	HB	1294/1451	(Q5)	1.23 (0.95–1.61)	0.26	46–74	[21]
Flavonols	Kaempferol	WNYDS	American	PB	433/538	< 1.4475 vs > 6.0568 (Q4)	0.83 (0.58–1.18)	0.80		[18]
Flavonols	Kaempferol		American	HB	83/107		0.77 (0.42–1.43)	0.41		[27]
Flavonols	Myricetin		American	HB	83/107		1.12 (0.61–2.06)	0.70		[27]
Flavonols	Quercetin	WNYDS	American	PB	433/538	< 10.5663 vs > 25.5626 (Q4)	0.64 (0.44–0.92)	0.15		[18]
Flavonols	Quercetin		American	HB	83/107		0.96 (0.53–1.76)	0.90		[27]
Flavanones			Italian	HB	1294/1451	(Q5)	0.96 (0.75–1.23)	0.56	46–74	[21]
Flavanols			Italian	HB	1294/1451	(Q5)	1.30 (1.01–1.69)	0.48	46–74	[21]
Isoflavones		EPIC-Norfolk	English	PB	203/800		0.89 (0.72–1.11)	0.29	40–79	[29]
Isoflavones			Italian	HB	1294/1451	(Q5)	0.98 (0.76–1.26)	0.34	46–74	[21]
Isoflavones		PCANDIET	Scottish	PB	433/483	< 0.5811 vs > 1.9828 (Q4)	1.18 (0.79–1.75)	0.87	50–74	[5]
Isoflavones		CAPS	Swedish	PB	1499/1130	0.0008 vs 0.113 (Q4)	0.99 (0.77–1.28)	0.68	36–79	[17]
Isoflavones		CAPS	Swedish	PB	1431/1081	0.0008 vs 0.113 (Q4)	0.99 (0.77–1.28)	0.95	35–79	[28]
Isoflavones			Japanese	HB	200/200	< 30.5 vs ≥ 89.9 (Q4)	0.42 (0.24–0.72)	< 0.01*	59–73	[1]
Isoflavones	Genistein		American	HB	83/107		0.71 (0.39–1.30)	0.26		[27]
Isoflavones	Genistein	EPIC-Norfolk	English	PB	203/800		0.90 (0.74–1.10)	0.31	40–79	[29]
Isoflavones	Genistein	EPIC-Norfolk	English	PB	89/178		1.07 (0.84–1.37)	0.575	45–75	[12]
Isoflavones	Genistein	CAPS	Swedish	PB	1499/1130	0.00019 vs 0.0694 (Q4)	0.97 (0.75–1.26)	0.09	36–79	[17]
Isoflavones	Genistein		Chinese	PB	133/265	< 17.9 vs > 62.0 (Q4)	0.53 (0.29–0.97)	0.058	50–89	[15]
Isoflavones	Genistein		Japanese	HB	200/200	< 1.1 vs ≥ 2.5 (Q4)	0.58 (0.34–0.97)	0.04*	59–73	[1]
Isoflavones	Daidzein		American	HB	83/107		0.57 (0.31–1.05)	0.07		[27]
Isoflavones	Daidzein	EPIC-Norfolk	English	PB	203/800		0.92 (0.69–1.22)	0.56	40–79	[29]
Isoflavones	Daidzein	EPIC-Norfolk	English	PB	89/178		1.06 (0.84–1.64)	0.630	45–75	[12]
Isoflavones	Daidzein	CAPS	Swedish	PB	1499/1130	0.00037 vs 0.0431 (Q4)	1.22 (0.92–1.62)	0.70	36–79	[17]
Isoflavones	Daidzein		Chinese	PB	133/265	< 10.0 vs > 36.3 (Q4)	0.56 (0.31–1.04)	0.116	50–89	[15]
Isoflavones	Daidzein		Japanese	HB	200/200	< 0.8 vs ≥ 1.9 (Q4)	0.55 (0.32–0.93)	0.02*	59–73	[1]
Isoflavones	Biochanin A		American	HB	83/107		0.92 (0.50–1.70)	0.79		[27]
Isoflavones	Biochanin A	EPIC-Norfolk	English	PB	203/800		0.89 (0.69–1.14)	0.34	40–79	[29]
Isoflavones	Formononetin		American	HB	83/107		0.99 (0.54–1.81)	0.98		[27]
Isoflavones	Formononetin	EPIC-Norfolk	English	PB	203/800		0.97 (0.83–1.13)	0.70	40–79	[29]
Isoflavones	Glycitein	EPIC-Norfolk	English	PB	203/800		0.88 (0.67–1.15)	0.34	40–79	[29]
Isoflavones	Equol	EPIC-Norfolk	English	PB	203/800		1.31 (1.00–1.71)	0.050*	40–79	[29]
Anthocyanidins			Italian	HB	1294/1451		1.18 (0.91–1.53)	0.22	46–74	[21]

Note: ^aCAPS – The Cancer Prostate Sweden Study; EPIC – The European Prospective Investigation into Cancer and Nutrition; PCANDIET – The Prostate Cancer and Diet Study; WNYDS – The Western New York Diet Study.

^bHB – hospital-based; PB – population-based.

^cQ4 – quartiles; Q5 – quintiles.

^dOR – odds ratio; RR – relative risk.

^eStatistically significant effects (p for trend < 0.05) are marked by asterisk.

of both genistein and daidzein against prostate cancer. At that, Nagata *et al.* described a significant 42% and 45% reduction of prostate cancer risk with high dietary consumption of genistein and daidzein, respectively [1], and Lee *et al.* reported a 47% and 44% decrease in the tumor risk with high consumption of these isoflavones, respectively [15]. These results demonstrate that isoflavones can indeed contribute to a protective effect against prostate neoplasms. Also, Strom *et al.* observed some suggestive, still non-significant, lowering in prostate cancer incidence with high dietary consumption of daidzein and genistein among American men [27]. As the daily intake of soy foods in European countries is very low compared to Asian men (this difference can be even about hundredfold), it is possible that these levels were too low for a preventive effect against prostate cancer to be become obvious [12, 21] (see Table 1).

Prospective cohort studies

Using the prospective cohort study design, no significant inverse associations with prostate cancer risk were found for intake of total flavonoids as well as flavonoid subclasses flavones, flavanones and anthocyanidins in different populations, including American, Hawaiian, Dutch, and Finnish men [23, 30–33]. Although Wang *et al.* observed a weak positive relationship with intake of total flavonoids, flavanols or isoflavones, but also

flavonols or flavanones with overall prostate cancer incidence, the relative risk varied over follow-up time and the positive association disappeared when the cases diagnosed during the first two follow-up years were excluded from the analysis [16]. The authors proposed that such pattern could be affected by behaviors associated with prostate cancer screening [16]. For flavonols, Knekt *et al.* found a statistically significant 57% decrease in prostate cancer risk with high dietary intake of myricetin among Finnish men; but no risk modification by other common flavonols like kaempferol or quercetin [31]. Geybels *et al.* conducted a prospective cohort study with Dutch men and stratification of the analysis by cancer stage revealed a significant inverse association between intake of both kaempferol and myricetin (not quercetin) with stage IV prostate cancer and not with overall or non-advanced neoplasms (stage I/II tumors) [33]. Similar trend became evident also for total flavanols and epicatechin (not catechin), as the significant inverse association was found for advanced stage prostate tumor and not non-advanced cancer [33].

Although both Park *et al.* and Kurahashi *et al.* reported no significant relationships between intake of individual isoflavones (genistein, daidzein) and total prostate cancer risk [3, 23], Kurahashi *et al.* still found

Table 2. Epidemiological prospective cohort studies on dietary intake of flavonoids and prostate cancer risk

Flavonoid subclass	Certain compound	Study ^a	Population	Median follow-up (years)	Cases/cohort	Intake comparison (low vs high, mg/day) ^b	Multivariate-adjusted RR/HR ^c	<i>p</i> for trend ^d	Comments ^e	Reference
Flavonoids		CPS-II	American	7.8	3974/43,268	< 126.6 vs ≥ 359.5 (Q5)	1.11 (1.01–1.23)	0.02*	50–74 y; positive association for high grade cancer within the first 2 y of follow-up, suggestive inverse association after excluding these first 2 y; no associations with advanced cancer	[16]
Flavonoids		MEC	American, Hawaiian	8.0	4404/82,483	< 1.6 vs ≥ 7.2/1000 kcal (Q5)	0.93 (0.83–1.04)	0.17	45–75 y; multiethnic; no inverse association regardless of stage	[23]
Flavonoids		NLCS	Dutch	17.3	3362/58,279	13.1 vs 40.6 (Q4)	1.00 (0.84–1.18)	0.74	55–69 y; no significant effect modification by cancer stage	[33]
Flavonoids		FMC	Finnish	24.0	62/9959	< 2.1 vs > 4.8 (Q4)	1.39 (0.56–3.46)		15–99 y	[30]
Flavonoids		FMC	Finnish	30.0	95/5218	4.3 vs 26.9 (Q4)	1.11 (0.61–2.01)	0.57		[31]
Flavonoids		KIHD	Finnish	16.2	138/2590	9.1 vs 416.3 (Q4)	1.16 (0.58–2.34)	0.831	42–60 y	[32]
Flavones		CPS-II	American	7.8	3974/43,268	< 0.5 vs ≥ 2.2 (Q5)	1.05 (0.95–1.16)	0.19	50–74 y; no associations for high grade or advanced cancers within or without the first 2 y of follow-up	[16]
Flavones		KIHD	Finnish	16.2	138/2590	(Q4)	0.71 (0.30–1.65)	0.561	42–60 y	[32]
Flavonols		CPS-II	American	7.8	3974/43,268	< 8.9 vs ≥ 20.5 (Q5)	1.10 (0.99–1.21)	0.05*	50–74 y; suggestive positive association for high grade cancer within the first 2 y of follow-up, not after excluding these first 2 y; no associations with advanced cancer	[16]
Flavonols		KIHD	Finnish	16.2	138/2590	(Q4)	1.53 (0.72–3.23)	0.585	42–60 y	[32]
Flavonols	Kaempferol	NLCS	Dutch	17.3	3362/58,279	2.5 vs 11.2 (Q4)	0.98 (0.83–1.16)	0.73	55–69 y; significant inverse association for stage IV cancer [0.78 (0.61–1.00), <i>p</i> = 0.03*], not for non-advanced cancer	[33]
Flavonols	Kaempferol	FMC	Finnish	30.0	95/5218	0.1 vs 0.8 (Q4)	1.03 (0.53–2.02)	0.54		[31]
Flavonols	Myricetin	NLCS	Dutch	17.3	3362/58,279	0.4 vs 2.6 (Q4)	0.89 (0.75–1.05)	0.41	55–69 y; significant inverse association for stage IV cancer [0.71 (0.55–0.91), <i>p</i> = 0.03*], not for non-advanced cancer	[33]
Flavonols	Myricetin	FMC	Finnish	30.0	95/5218	0 vs 0.11 (Q4)	0.43 (0.22–0.86)	0.002*		[31]
Flavonols	Quercetin	NLCS	Dutch	17.3	3362/58,279	8.8 vs 28.5 (Q4)	1.01 (0.85–1.19)	0.98	55–69 y; no significant effect modification by cancer stage	[33]
Flavonols	Quercetin	FMC	Finnish	30.0	95/5218	1.5 vs 3.9 (Q4)	0.76 (0.40–1.42)	0.35		[31]
Flavanones		CPS-II	American	7.8	3974/43,268	< 7.5 vs ≥ 38.2 (Q5)	1.08 (0.98–1.20)	0.31	50–74 y; positive association for high grade cancer within the first 2 y of follow-up, not after excluding these first 2 y; no associations with advanced cancer	[16]
Flavanones		KIHD	Finnish	16.2	138/2590	(Q4)	0.90 (0.37–2.20)	0.518	42–60 y	[32]
Flavanones	Hesperetin	FMC	Finnish	30.0	95/5218	0 vs 15.4 (Q4)	1.47 (0.80–2.71)	0.26		[31]
Flavanones	Naringenin	FMC	Finnish	30.0	95/5218	0 vs 4.7 (Q4)	1.48 (0.80–2.73)	0.27		[31]
Flavanols		CPS-II	American	7.8	3974/43,268	< 10.4 vs ≥ 37.9 (Q5)	1.18 (1.06–1.30)	0.01*	50–74 y; suggestive positive association for high grade cancer within the first 2 y of follow-up, not after excluding these first 2 y; no associations with advanced cancer	[16]
Flavanols		NLCS	Dutch	17.3	3362/58,279	14.5 vs 98.7 (Q4)	0.97 (0.82–1.15)	0.58	55–69 y; significant inverse association for stage IV cancer [0.73 (0.57–0.95), <i>p</i> = 0.01*], not for non-advanced cancer	[33]
Flavanols		KIHD	Finnish	16.2	138/2590	(Q4)	1.37 (0.65–2.89)	0.82	42–60 y	[32]
Flavanols	Catechin	NLCS	Dutch	17.3	3362/58,279	1.9 vs 6.8 (Q4)	1.03 (0.88–1.22)	0.83	55–69 y; no significant effect modification by cancer stage	[33]

Flavonoid subclass	Certain compound	Study ^a	Population	Median follow-up (years)	Cases/cohort	Intake comparison (low vs high, mg/day) ^b	Multivariate-adjusted RR/HR ^c	<i>p</i> for trend ^d	Comments ^e	Reference
Flavanols	Epicatechin	NLCS	Dutch	17.3	3362/58,279	5.3 vs 20.8 (Q4)	1.01 (0.86–1.20)	0.62	55–69 y; significant inverse association for stage III/IV [0.84 (0.68–1.04), <i>p</i> = 0.05*] and IV cancer [0.74 (0.57–0.95), <i>p</i> = 0.01*], not for non-advanced cancer	[33]
Isoflavones		CPS-II	American	7.8	3974/43,268	< 0.029 vs ≥ 0.144 (Q5)	1.11 (1.01–1.22)	<0.001*	50–74 y; no associations for high grade or advanced cancers within or without the first 2 y of follow-up	[16]
Isoflavones	Genistein	MEC	American, Hawaiian	8.0	4404/82,483	< 0.7 vs ≥ 3.1/1000 kcal (Q5)	0.94 (0.84–1.04)	0.16	45–75 y; multiethnic; no inverse association regardless of stage	[23]
Isoflavones	Genistein	JPHC	Japanese	5.0	307/43,509	< 13.2 vs ≥ 32.8 (Q4)	0.71 (0.48–1.03)	0.22	45–74 y; non-significant inverse association for localized, not advanced cancer; significant inverse association for men > 60 y with localized cancer [0.52 (0.30–0.90), <i>p</i> = 0.03*], not advanced cancer or for younger men	[3]
Isoflavones	Daidzein	MEC	American, Hawaiian	8.0	4404/82,483	< 0.7 vs ≥ 3.2/1000 kcal (Q5)	0.92 (0.82–1.02)	0.09	45–75 y; multiethnic; no inverse association regardless of stage	[23]
Isoflavones	Daidzein	JPHC	Japanese	5.0	307/43,509	< 8.5 vs ≥ 20.4 (Q4)	0.77 (0.52–1.13)	0.43	45–74 y; non-significant inverse association for localized, not advanced cancer; significant inverse association for men > 60 y with localized cancer [0.50 (0.28–0.88), <i>p</i> = 0.04*], not advanced cancer or for younger men	[3]
Isoflavones	Glycitein	MEC	American, Hawaiian	8.0	4404/82,483	< 0.18 vs ≥ 0.80/1000 kcal (Q5)	0.91 (0.82–1.01)	0.07	45–75 y; multiethnic; no inverse association regardless of stage	[23]
Anthocyanidins		CPS-II	American	7.8	3974/43,268	< 5.9 vs ≥ 18.0 (Q5)	1.10 (1.00–1.22)	0.13	50–74 y; no associations for high grade or advanced cancers within or without the first 2 y of follow-up	[16]
Anthocyanidins		KIHD	Finnish	16.2	138/2590	(Q4)	0.59 (0.24–1.41)	0.974	42–60 y	[32]

Note: ^aCPS-II – The Cancer Prevention Study II Nutrition Cohort; FMC – The Finnish Mobile Clinic Health Examination Survey; JPHC – The Japan Public Health Center-based prospective study; KIHD – The Kuopio Ischaemic Heart Disease Risk Factor Study; MEC – The Multiethnic Cohort Study; NLCS – The Netherlands Cohort Study.

^bQ4 – quartiles; Q5 – quintiles.

^cRR – relative risk; HR – hazard ratio.

^dStatistically significant effects (*p* for trend < 0.05) are marked by asterisk.

^eAge in baseline.

an inverse association between intake of both genistein and daidzein and localized cancer [3]. In particular, Japanese men older than 60 years had about 50% lower risk of localized prostate cancer with high dietary consumption of genistein and daidzein [3] (see Table 2). Thus, compared to findings from case-control studies, the evidence from prospective cohort studies about the protective effects of flavonoids against prostate cancer is much more sparse being restricted to certain subgroups (stratified by age of subjects or cancer stage).

Biomarker studies

Unlike the works assessing retrospectively or prospectively dietary intake of different flavonoids, biomarker studies have focused only to isoflavones and their metabolites. At that, no associations were observed between total serum or urinary isoflavones and prostate cancer risk in English [34] or Scottish men [5].

Null associations were detected also for individual serum isoflavones and their urinary biomarkers (genistein, daidzein, glycitein, O-desmethylangolensin, equol) within English men [12, 34] and for serum isoflavones among older Scottish men [5]. In a large prospective investigation performed with men from eight European countries, no significant relationship was reported for plasma genistein, daidzein or equol and prostate cancer risk [24, 35]. In the work conducted with Jamaican men, no association was found between urinary excretion of genistein or daidzein and prostate cancer incidence, but a significant inverse relationship was found for urinary equol concentration when non-producers of equol were assessed as reference group [36]. This study indicated that men who were able to produce equol from daidzein by the aid of specific intestinal microflora were at reduced risk of total and high grade (but not low

Table 3. Epidemiological studies on biomarkers of flavonoids and prostate cancer risk

Flavonoid subclass	Certain compound	Bio-marker	Study ^a	Popula-tion	Cases/controls	Multivariate-adjusted OR/RR ^b	<i>p</i> for trend ^c	Comments ^d	Reference
Isoflavones		Serum	EPIC-Norfolk	English	191/815	1.01 (0.93–1.10)	0.809	45–75 y	[34]
Isoflavones		Serum	PCANDIET	Scottish	238/198	1.24 (0.69–2.20)	0.64	50–74 y	[5]
Isoflavones		Urinary	EPIC-Norfolk	English	152/665	0.98 (0.90–1.08)	0.727	45–75 y	[34]
Isoflavones	Genistein	Plasma	EPIC	European	1605/1697	1.00 (0.79–1.27)	0.82	43–76 y; from eight countries; no associations as stratified by cancer stage (localized or advanced) or histological grade (low or high), or age of men at diagnosis (< 60 y or ≥ 60 y)	[35]
Isoflavones	Genistein	Plasma	EPIC	European	950/1042	0.74 (0.54–1.00)	0.051*	43–76 y; from eight countries	[24]
Isoflavones	Genistein	Plasma	JPHC	Japanese	201/402	0.66 (0.40–1.08)	0.08	40–69 y; significant inverse association for localized cancer [0.54 (0.29–1.01), <i>p</i> = 0.03*], not advanced cancer	[5]
Isoflavones	Genistein	Serum	JACC	Japanese	52/151	0.76 (0.32–1.82)	0.54	≥ 40 y; suggestive inverse association for men with T ≥ 6.9 nM, or T ≥ 6.9 nM and PSA ≤ 10 ng/ml for cases, < 4 ng/ml for controls	[25]
Isoflavones	Genistein	Plasma		Chinese	46/54	0.31 (0.13–0.71)	0.006*		[4]
Isoflavones	Genistein	Serum	EPIC-Norfolk	English	191/815	0.99 (0.93–1.05)	0.78	45–75 y	[34]
Isoflavones	Genistein	Serum	EPIC-Norfolk	English	89/178	1.01 (0.83–1.23)	0.938	45–75 y	[12]
Isoflavones	Genistein	Serum	PCANDIET	Scottish	238/198	1.36 (0.76–2.43)	0.37	50–74 y	[5]
Isoflavones	Genistein	Urinary	MEC	American, Hawaiian	249/404	0.72 (0.40–1.31)	0.09	45–75 y; multiethnic; suggestive inverse association for localized and advanced cancer, and for Latinos and Whites (not African Americans and Japanese Americans)	[37]
Isoflavones	Genistein	Urinary		Jamaican	175/194	1.23 (0.67–2.56)	0.502	40–80 y; no associations as stratified by cancer grades (low or high)	[36]
Isoflavones	Genistein	Urinary	EPIC-Norfolk	English	152/665	1.00 (0.95–1.05)	0.86	45–75 y	[34]
Isoflavones	Genistein	Urinary	EPIC-Norfolk	English	89/178	0.92 (0.76–1.12)	0.415	45–75 y	[12]
Isoflavones	Daidzein	Plasma	EPIC	European	950/1042	0.80 (0.60–1.07)	0.209	43–76 y; from eight countries	[24]
Isoflavones	Daidzein	Plasma	JPHC	Japanese	201/402	0.78 (0.49–1.25)	0.44	40–69 y; suggestive inverse association for localized, not advanced cancer	[6]
Isoflavones	Daidzein	Serum	EPIC-Norfolk	English	89/178	1.01 (0.86–1.18)	0.902	45–75 y	[12]
Isoflavones	Daidzein	Serum	EPIC-Norfolk	English	191/815	0.99 (0.93–1.05)	0.68	45–75 y	[34]
Isoflavones	Daidzein	Serum	PCANDIET	Scottish	247/200	1.34 (0.76–2.38)	0.21	50–74 y	[5]
Isoflavones	Daidzein	Serum	JACC	Japanese	52/151	0.74 (0.31–1.76)	0.50	≥ 40 y; suggestive inverse association for men with T ≥ 6.9 nM, or T ≥ 6.9 nM and PSA ≤ 10 ng/ml for cases, < 4 ng/ml for controls	[25]
Isoflavones	Daidzein	Urinary	MEC	American, Hawaiian	249/404	0.55 (0.31–0.98)	0.03*	45–75 y; multiethnic; suggestive inverse associations for localized and advanced cancer, and for different ethnic groups (African Americans, Japanese Americans, Latinos and Whites)	[37]
Isoflavones	Daidzein	Urinary		Jamaican	175/194	0.85 (0.47–1.54)	0.600	40–80 y; no associations as stratified by cancer grades (low or high)	[36]
Isoflavones	Daidzein	Urinary	EPIC-Norfolk	English	152/665	0.97 (0.92–1.03)	0.31	45–75 y	[34]
Isoflavones	Daidzein	Urinary	EPIC-Norfolk	English	89/178	0.99 (0.83–1.17)	0.866	45–75 y	[12]
Isoflavones	Glycitein	Plasma	JPHC	Japanese	201/402	0.78 (0.48–1.26)	0.51	40–69 y; no associations as stratified by cancer stage (localized or advanced)	[6]
Isoflavones	Glycitein	Serum	EPIC-Norfolk	English	191/815	1.01 (0.95–1.08)	0.67	45–75 y	[34]
Isoflavones	Glycitein	Serum	EPIC-Norfolk	English	89/178	1.08 (0.49–2.38)	0.848	45–75 y	[12]
Isoflavones	Glycitein	Urinary	EPIC-Norfolk	English	152/665	1.01 (0.96–1.06)	0.81	45–75 y	[34]
Isoflavones	Glycitein	Urinary	EPIC-Norfolk	English	89/178	1.01 (0.82–1.26)	0.901	45–75 y	[12]
Isoflavones	O-Des-methylangolensin	Serum	EPIC-Norfolk	English	191/815	0.97 (0.91–1.03)	0.33	45–75 y	[34]
Isoflavones	O-Des-methylangolensin	Serum	EPIC-Norfolk	English	89/178	0.68 (0.36–1.29)	0.236	45–75 y	[12]
Isoflavones	O-Des-methylangolensin	Urinary	EPIC-Norfolk	English	152/665	0.98 (0.94–1.03)	0.42	45–75 y	[34]
Isoflavones	O-Des-methylangolensin	Urinary	EPIC-Norfolk	English	89/178	0.93 (0.73–1.18)	0.540	45–75 y	[12]
Isoflavones	Equol	Plasma	EPIC	European	950/1042	0.99 (0.70–1.39)	0.461	43–76 y; from eight countries	[24]
Isoflavones	Equol	Plasma	JPHC	Japanese	201/402	0.60 (0.36–0.99)	0.04*	40–69 y; significant inverse association for localized cancer [0.43 (0.22–0.82), <i>p</i> = 0.02*], not advanced cancer	[6]
Isoflavones	Equol	Serum	EPIC-Norfolk	English	191/815	1.02 (0.96–1.08)	0.52	45–75 y	[34]
Isoflavones	Equol	Serum	EPIC-Norfolk	English	89/178	1.32 (0.73–2.38)	0.358	45–75 y	[12]
Isoflavones	Equol	Serum	PCANDIET	Scottish	247/200	1.07 (0.71–1.61)	0.75	50–74 y	[5]
Isoflavones	Equol	Serum	JACC	Japanese	52/151	0.39 (0.15–0.98)	0.046*	≥ 40 y; suggestive inverse association for men with T ≥ 6.9 nM, or T ≥ 6.9 nM and PSA ≤ 10 ng/ml for cases, < 4 ng/ml for controls	[25]
Isoflavones	Equol	Urinary	MEC	American, Hawaiian	249/404	1.32 (0.84–2.08)	0.08	45–75 y; multiethnic; no associations for localized and advanced cancer or different ethnic groups (African Americans, Japanese Americans, Latinos and Whites)	[37]

Flavonoid subclass	Certain compound	Bio-marker	Study ^a	Population	Cases/controls	Multivariate-adjusted OR/RR ^b	<i>p</i> for trend ^c	Comments ^d	Reference
Isoflavones	Equol	Urinary		Jamaican	175/194	0.48 (0.26–0.87)	0.020*	40–80 y; significant inverse association for high grade cancer [0.29 (0.13–0.60), <i>p</i> = 0.001*], not low grade cancer	[36]
Isoflavones	Equol	Urinary	EPIC-Norfolk	English	152/665	1.03 (0.97–1.07)	0.20	45–75 y	[34]
Isoflavones	Equol	Urinary	EPIC-Norfolk	English	89/178	1.21 (0.93–1.57)	0.147	45–75 y	[12]

Note: ^aEPIC – The European Prospective Investigation into Cancer and Nutrition; JACC – The Japan Collaborative Cohort Study; JPHC – The Japan Public Health Center-based Prospective Study; MEC – The Multiethnic Cohort Study; PCANDIET – The Prostate Cancer and Diet Study.

^bOR – odds ratio; RR – relative risk; the risk for equol is presented in comparison to equol non-producers.

^cStatistically significant effects (*p* for trend < 0.05) are marked by asterisk.

^dPSA – prostate-specific antigen; T – testosterone.

grade) prostate cancer as compared to non-producers of this metabolite [36]. However, another study that measured urinary biomarkers of isoflavones did not observe such protective effect for equol [37]. Quite contrary, urinary excretion of daidzein was significantly inversely associated with prostate cancer risk among multiethnic men living in Hawaii and Los Angeles and a respective suggestive trend was indicated also for genistein, regardless of the stage of tumor [37].

Differently from works performed with European and American men, their Asian counterparts consume substantially higher amounts of soy foods and consequently also isoflavones. Wu *et al.* reported a 69% reduced prostate cancer risk among Chinese men consuming high amounts of genistein as evaluated by plasma genistein level [4]. Kurahashi *et al.* described a significant 44% reduction in the risk of localized (not advanced) prostate tumor among Japanese men with higher plasma genistein concentrations and a similar suggestive tendency was reported also for plasma daidzein level [6]. Plasma equol level was inversely related to both overall as well as localized prostate cancer incidence, not modifying the risk of advanced cancer [6]. A significant 61% decrease in prostate cancer risk was detected also in another study with Japanese men with high serum equol levels and similar suggestive, still non-significant, trend was observed for genistein and daidzein when the subjects with low serum testosterone levels were excluded [25]. These studies with Asian men support that high doses of isoflavones can be indeed preventive against prostate cancer development (see Table 3).

POTENTIAL FACTORS GIVING RISE TO INCONCISTENCIES

As come into sight from the epidemiological findings presented in above paragraphs, there are still relatively few data published about the associations between flavonoids and prostate cancer risk, and these results are rather inconclusive. There are several potential reasons providing some explanations to these inconsistencies.

First, assessment of intake of flavonoids has been limited for a long time due to lack of data about food composition. Exposure to flavonoids can be estimated by either food diaries or food frequency questionnaires and these data are further translated to dietary intake using quantitative food composition databases [12]. However, reliable information about the content of flavonoids in different plant-derived food items was not available until the last decade, when several databases

were made public for scientific community [16, 21, 23]. However, these food composition databases are not able to capture the variability of flavonoid content attributable to cultivars, growing methods and environmental conditions, exposure to sunlight and heat, or harvesting time and processing practices [21, 33, 38]. Also, these data tables can not detect all sources of flavonoids in the human diet [37]. Furthermore, some questions arise by adaptation of food composition databases created in the US to the diet consumed in European countries [5, 21].

Second, another possible reason for the inconsistent results of epidemiological studies can come from the differences in level of flavonoids intake. For example, it has been demonstrated that the mean daily consumption of isoflavones is low in Western populations (< 3 mg), whereas it is considerably higher among Asian subjects reaching even 70–100 mg and being for most Asian men in the range of 30 to 50 mg [1, 4, 5, 7, 15–17, 23]. Therefore, it can be that the consumption of isoflavones in Western countries is too low to observe a protective action against prostate tumor [4, 5, 9, 10, 12, 16, 23, 35]. Whether similar effects exist also for other flavonoids and their subclasses, *i.e.* the risk-lowering response manifests only at a certain level, is still unknown. The possible age periods of the highest susceptibility to beneficial effects of flavonoids have also remained to be determined. Furthermore, we can not rule out the possibility that follow-up times of prospective cohort studies were not long enough for detection of protective action, especially in the case of advanced neoplasms [16].

Third, it is well known that following to their ingestion, flavonoids undergo an extensive metabolic conversion in the intestine and liver, as a result of which various conjugates with potentially altered biological activity enter bloodstream and reach target tissues, and are finally excreted in urine [11, 12]. Blood and urinary biomarkers can reflect dietary consumption of flavonoids, capturing intake from all food sources, considering also their metabolic biotransformation [24, 34]. Therefore, direct measurement of these biomarkers might provide a more relevant insight into the associations between exposure to flavonoids and prostate cancer risk than assessment of food consumption [34]. However, besides dietary intake, the levels of flavonoids in biological fluids are affected by intestinal microflora, diet composition and content of fat in the food, consumption of alcohol, and the use of antibiotics as well as possible bowel diseases [5, 28, 36]. Moreover, biomarkers reflect only

short-term intake of flavonoids due to their brief half-lives in the human body and might not accurately reflect the long-term dietary habits; especially, when only one serum measurement or spot urine test is used [2, 5, 6, 35–37]. Thus, estimation of dietary intake has remained indispensable in epidemiological studies, whereas measurement of biomarkers can complement dietary assessment with bioavailability issues. At that, about 30–50% of people are able to metabolize daidzein to equol, the most biologically active isoflavone, by the aid of special intestinal bacteria and this ability varies within different ethnic populations [8, 9, 19, 36, 38]. Moreover, it has been shown that the prevalence of equol-producers is generally lower among subjects suffering from prostate cancer compared to healthy controls [2, 8, 19]. For example, it was shown that just 29% of Japanese men with prostate cancer could produce equol, compared to 46% of controls and these estimates were 30% and 59% for Korean cases and controls, respectively [8]. If further studies confirm that equol can lower the prostate cancer risk and intestinal environment without equol-converting bacteria is indeed a risk factor for this malignancy, a possible prevention strategy for future would be to improve intestinal microflora by probiotic technology, enabling it to generate equol [7, 9].

In the case of retrospective study design, the recall bias is unavoidable. Patients could recall their food consumption differently than controls and it is also possible that they changed their diet after cancer was diagnosed [15, 21]. However, this misclassification was probably non-differential, as the knowledge about possible role of flavonoids on prostate carcinogenesis was not widespread among general public [15, 28]. Analysis of data collected prospectively might reduce the problems of disease-related influences on dietary intake of flavonoid-rich food items or their biomarker levels [34, 37]. However, the number of cases could not be large enough for acceptably strong statistical power, especially for subgroup analyses stratified by different parameters [19, 33, 37].

Another common concern in epidemiological studies is potential confounding. Despite adjustment for diverse aspects, it is always possible that residual confounders due to uncontrolled or as yet unknown factors might remain [5, 12, 15, 16, 26, 27, 36]. For example, most of the studies did not collect information about testing of prostate specific antigen that might be a confounder [16, 33]. Also, only few investigations considered histological grade or tumor stage, although risk factors of prostate cancer can vary within subgroups differentiated by disease aggressiveness or stage [8, 26, 33]. In addition, lifestyle related to consumption of higher doses of flavonoids or some dietary covariates might contribute to the susceptibility to prostate carcinogenesis [3, 5, 10, 16]. Furthermore, Hedelin *et al.* indicated that health benefits of isoflavone intake against prostate tumor can be restricted to men carrying specific genetic variant in estrogen receptor β gene [28].

CONCLUSIONS AND FURTHER PERSPECTIVES

High incidence rate, slow progression and long course make prostate cancer a perfect disorder for chemoprevention which onset, development and progression can be influenced by certain dietary constituents [20]. There are several epidemiological findings suggesting that high intake of specific flavonoids can lead to reduced prostate cancer risk. Indeed, consumption of isoflavones at doses characteristic to Asian population may modulate the risk of prostate cancer and therefore, high intake of these phytoestrogens might be an efficient protective means against prostate tumorigenesis among Chinese and Japanese men. The stronger preventive effect of isoflavones on localized tumor compared to advanced neoplasm is in agreement with the expression of estrogen receptor β in normal prostate tissue and early stages neoplasm, decline in expression during malignant transformation and complete loss in advanced tumor with higher metastatic potential and mortality; supposing that preventive effects of isoflavones are mediated via this receptor subtype [3, 6, 28]. Based on the autopsy studies the rate of latent tumors is similar in Asian and Western countries and the significantly lower incidence of clinically detectable prostate tumors in Asian men can come from blocking and delaying the latent cancer progression by intake of high amounts of isoflavones [3, 6]. An important factor in health benefits of high consumption of isoflavones seems to arise also from the ability to metabolize daidzein to equol by possessing a specific intestinal bacterial combination. Whether ethnic variation in this metabolic conversion may provide some explanation to the differences in prostate cancer incidence remains to be further clarified. On the other hand, some epidemiological studies with Western men have demonstrated the protective action of certain flavonols or flavanols manifesting particularly against advanced, later stage tumor. As a whole, these data indicate that through intake of various plant-derived phytochemicals nature can provide protection and chemoprevention against different stages of prostate cancer.

There is no doubt that large-scale and preferentially prospectively designed studies are needed to further investigate the association between exposure to flavonoids and the risk of prostate cancer. At that, subjects with consumption of wider concentration range of these plant metabolites as well as stratification by different factors, including disease stage, are highly needed. If the protective effects will be confirmed, chemopreventive intervention strategies via modification of dietary habits can be developed to reduce the prostate cancer incidence, especially among at-risk men. Last but not least, although adverse effects of flavonoids on the prostate tissue have not been reported, studies considering safety profile of these phytochemicals are never too much.

CONFLICT OF INTEREST

None declare.

REFERENCES

1. Nagata Y, Sonoda T, Mori M, *et al.* Dietary isoflavones may protect against prostate cancer in Japanese men. *J Nutr* 2007; **137**: 1974–9.
2. Akaza H, Miyanaga N, Takashima N, *et al.* Comparisons of percent equol producers between prostate cancer patients and controls: case-controlled studies of isoflavones in Japanese, Korean and American residents. *Jpn J Clin Oncol* 2004; **34**: 86–9.
3. Kurahashi N, Iwasaki M, Sasazuki S, *et al.* Soy product and isoflavone consumption in relation to prostate cancer in Japanese men. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 538–45.
4. Wu Y, Zhang L, Na R, *et al.* Plasma genistein and risk of prostate cancer in Chinese population. *Int Urol Nephrol* 2015; **47**: 965–70.
5. Heald CL, Ritchie MR, Bolton-Smith C, *et al.* Phytoestrogens and risk of prostate cancer in Scottish men. *Br J Nutr* 2007; **98**: 388–96.
6. Kurahashi N, Iwasaki M, Inoue M, *et al.* Plasma isoflavones and subsequent risk of prostate cancer in a nested case-control study: the Japan Public Health Center. *J Clin Oncol* 2008; **26**: 5923–9.
7. Akaza H. Prostate cancer chemoprevention by soy isoflavones: role of intestinal bacteria as the “second human genome”. *Cancer Sci* 2012; **103**: 969–75.
8. Vastag B. Soy and prostate cancer study results mixed. *J Natl Cancer Inst* 2007; **99**: 1364–5.
9. Sugiyama Y, Masumori N, Fukuta F, *et al.* Influence of isoflavone intake and equol-producing intestinal flora on prostate cancer risk. *Asian Pac J Cancer Prev* 2013; **14**: 1–4.
10. Ganry O. Phytoestrogens and prostate cancer risk. *Prev Med* 2005; **41**: 1–6.
11. Nambiar D, Singh RP. Advances in prostate cancer chemoprevention: a translational perspective. *Nutr Cancer* 2013; **65** (Suppl 1): 12–25.
12. Low YL, Taylor JI, Grace PB, *et al.* Phytoestrogen exposure, polymorphisms in COMT, CYP19, ESR1, and SHBG genes, and their associations with prostate cancer risk. *Nutr Cancer* 2006; **56**: 31–9.
13. Johnson JJ, Bailey HH, Mukhtar H. Green tea polyphenols for prostate cancer chemoprevention: a translational perspective. *Phytomedicine* 2010; **17**: 3–13.
14. Messina MJ. Emerging evidence on the role of soy in reducing prostate cancer risk. *Nutr Rev* 2003; **61**: 117–31.
15. Lee MM, Gomez SL, Chang JS, *et al.* Soy and isoflavone consumption in relation to prostate cancer risk in China. *Cancer Epidemiol Biomarkers Prev* 2003; **12**: 665–8.
16. Wang Y, Stevens VL, Shah R, *et al.* Dietary flavonoid and proanthocyanidin intakes and prostate cancer risk in a prospective cohort of US men. *Am J Epidemiol* 2014; **179**: 974–86.
17. Hedelin M, Klint A, Chang ET, *et al.* Dietary phytoestrogen, serum enterolactone and risk of prostate cancer: the cancer prostate Sweden study (Sweden). *Cancer Causes Control* 2006; **17**: 169–80.
18. McCann SE, Ambrosone CB, Moysich KB, *et al.* Intakes of selected nutrients, foods, and phytochemicals and prostate cancer risk in western New York. *Nutr Cancer* 2005; **53**: 33–41.
19. Jian L. Soy, isoflavones, and prostate cancer. *Mol Nutr Food Res* 2009; **53**: 217–26.
20. Yang F, Song L, Wang H, *et al.* Quercetin in prostate cancer: Chemotherapeutic and chemopreventive effects, mechanisms and clinical application potential (Review). *Oncol Rep* 2015; **33**: 2659–68.
21. Bosetti C, Bravi F, Talamini R, *et al.* Flavonoids and prostate cancer risk: a study in Italy. *Nutr Cancer* 2006; **56**: 123–7.
22. Sak K. Cytotoxicity of dietary flavonoids on different human cancer types. *Pharmacogn Rev* 2014; **8**: 122–46.
23. Park SY, Murphy SP, Wilkens LR, *et al.* Legume and isoflavone intake and prostate cancer risk: The Multiethnic Cohort Study. *Int J Cancer* 2008; **123**: 927–32.
24. Travis RC, Spencer EA, Allen NE, *et al.* Plasma phytoestrogens and prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer* 2009; **100**: 1817–23.
25. Ozasa K, Nakao M, Watanabe Y, *et al.* Serum phytoestrogens and prostate cancer risk in a nested case-control study among Japanese men. *Cancer Sci* 2004; **95**: 65–71.
26. Guo K, Liang Z, Liu L, *et al.* Flavonoids intake and risk of prostate cancer: a meta-analysis of observational studies. *Andrologia* 2016; **48**: 1175–82.
27. Strom SS, Yamamura Y, Duphorne CM, *et al.* Phytoestrogen intake and prostate cancer: a case-control study using a new database. *Nutr Cancer* 1999; **33**: 20–5.
28. Hedelin M, Bälter KA, Chang ET, *et al.* Dietary intake of phytoestrogens, estrogen receptor-beta polymorphisms and the risk of prostate cancer. *Prostate* 2006; **66**: 1512–20.
29. Ward HA, Kuhnle GG, Mulligan AA, *et al.* Breast, colorectal, and prostate cancer risk in the European Prospective Investigation into Cancer and Nutrition-Norfolk in relation to phytoestrogen intake derived from an improved database. *Am J Clin Nutr* 2010; **91**: 440–8.
30. Knekt P, Järvinen R, Seppänen R, *et al.* Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. *Am J Epidemiol* 1997; **146**: 223–30.
31. Knekt P, Kumpulainen J, Järvinen R, *et al.* Flavonoid intake and risk of chronic diseases. *Am J Clin Nutr* 2002; **76**: 560–8.
32. Mursu J, Nurmi T, Tuomainen TP, *et al.* Intake of flavonoids and risk of cancer in Finnish men: The Kuopio Ischaemic Heart Disease Risk Factor Study. *Int J Cancer* 2008; **123**: 660–3.
33. Geybels MS, Verhage BA, Arts IC, *et al.* Dietary flavonoid intake, black tea consumption, and risk of overall and advanced stage prostate cancer. *Am J Epidemiol* 2013; **177**: 1388–98.
34. Ward H, Chapelais G, Kuhnle GG, *et al.* Lack of prospective associations between plasma and urinary phytoestrogens and risk of prostate or colorectal cancer in the European Prospective into Cancer-Norfolk study. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 2891–4.
35. Travis RC, Allen NE, Appleby PN, *et al.* Prediagnostic concentrations of plasma genistein and prostate cancer risk in 1605 men with prostate cancer and 1697 matched control participants in EPIC. *Cancer Causes Control* 2012; **23**: 1163–71.
36. Jackson MD, McFarlane-Anderson ND, Simon GA, *et al.* Urinary phytoestrogens and risk of prostate cancer in Jamaican men. *Cancer Causes Control* 2010; **21**: 2249–57.
37. Park SY, Wilkens LR, Franke AA, *et al.* Urinary phytoestrogen excretion and prostate cancer risk: a nested case-control study in the Multiethnic Cohort. *Br J Cancer* 2009; **101**: 185–91.
38. van Die MD, Bone KM, Williams SG, *et al.* Soy and soy isoflavones in prostate cancer: a systematic review and meta-analysis of randomized controlled trials. *BJU Int* 2014; **113**: E119–30.