Original Article

Dietary Phytoestrogen Scoring Database for Prostate Cancer Studies and Their Role in Prostate Cancer Risk

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ABSTRACT

OBJECTIVES: To create a dietary isoflavones scoring database for future use in cancer epidemiologic studies.
To investigate the role of isoflavones in aetiology of prostate cancer.
MATERIALS AND METHODS: A population based case- control study was conducted on 525 cases and 843 controls. To create an isoflavones scoring database, a creditable phytoestrogens database, and data from publications were used to create a mathematical computerised calculation program. Then after obtaining isoflavone intake for each individual, an unconditional logistic regression with various models was carried out.
RESULTS: There are 131 food items in the Food Frequency Question (FFQ). Isoflavones values have been assigned to 56 items out of 131. The results of the analysis to explore the role of isoflavones either as a continuous or quintile variable were not significant, not a single quintile of isoflavones showed any significant association with prostate cancer risk.
CONCLUSION: The isoflavones scoring database has been created. The analysis of the young prostate cancer study dataset and the role of isoflavones in disease aetiology has not shown a statistically significant association.

KEY WORDS: Phytoestrogens; Isoflavones; prostate cancer risk.

INTRODUCTION

Globally, prostate cancer is the second most frequently diagnosed cancer in men (914,000 new cases, 13.6% of the total) making it fifth most common cancer over all. It is more common in western countries as compared to Asian populations [1].

International variations in prostate cancer incidence have suggested the crucial role of a variety of environmental risk factors, particularly diet. The role of diet is well studied and supported by epidemiological studies such as ecological, case-control and cohort studies [2].

Phytoestrogens are naturally derived, non-steroidal chemical compounds [3] structurally similar to oestrogen 17 β- estradiol with oestrogen like biological activity [4].

Phytoestrogens may have a protective effect on many chronic diseases like bowel, breast, prostate and other forms of cancers, osteoporosis, cardiovascular diseases and on the symptoms related to menopause [5,6].

As the phytoestrogens have an oestrogen like effect, they may reduce androgenic stimulation of the prostate [7]. They are bound to cellular oestrogen receptors in various organs with higher affinity to oestrogen receptor β (ERβ) as compared to oestrogen receptor α (ERα) [8].

Phytoestrogens are classified in to three main groups- flavonoids, coumestans and lignans. The flavonoids are again divided into three groups- flavones, flavanones and isoflavones [3]. In the UK diet, the main phytoestrogens consumed are isoflavones [9] and more than 90% of isoflavones in diet comprise genistein and diadzein [10]. Krazeisen and colleagues suggested that phytoestrogens may change hormonal concentration by acting as chemopreventive agents [3]. Since human endocrine system is very complex and delicate, ingestion of the phytoestrogens may interfere the system in following three ways:

Phytoestrogens might act like endogenous hormones
1- By exerting agonistic or antagonistic effects, at the hormone receptors.
2- By affecting the levels of active steroids, at key enzymes of hormone metabolism. OR
3-They may have variety of non-hormonal effects [3].

Phytoestrogens are currently being extensively investigated through the molecular, preclinical and clinical studies to determine their potential health benefits. Little work has been done to examine the effects of phytoestrogen on humans. In the absence of concrete data from the clinical trials, one has to rely in vitro and animal studies.

In this study, the focus is on isoflavones (one class of phytoestrogens), because isoflavones are phytoestrogens commonly found in the British diet and a validated isoflavones database containing 6000 British food items is already available [10].

Objectives

To create a dietary isoflavones scoring database for

FFQ for future use in cancer epidemiological studies.
To investigate the role of isoflavones in prostate cancer aetiology.

METHODS

The Gene- environment interactions in prostate cancer study is an ongoing population based case-control study covering selected regions of the UK. Ethical approval was granted by Trent Multicentre Research Ethics Committee on 14th May 1999.
Cases were men aged ≤ 60 years, with clinically diagnosed prostate cancer (ICD 10: C 61), selected through the British Association of Urological Surgeon's database (BAUS).
The controls were randomly selected age matched men from GP practices, not diagnosed with prostate cancer. A self-administered postal questionnaire was sent to cases and controls.
A Phytoestrogen values search was performed using the Pubmed search engine and of websites listing isoflavone values. The reference source is a publication by Ritchie et al [10]. After creating the database on isoflavones, analyses were carried out on the secondary dataset available from the case-control study on Gene-environmental interaction in prostate cancer.

Statistical analysis

Statistical analysis was done by using SPSS version 16.
A cut off value of 5% was selected for the statistical significance level i.e. confidence interval does not span 1 and p value <0.05.

Analysis of dataset

To compare the demographic characteristics of cases and controls, univariate logistic regressions were performed. The total isoflavone intake of all study subjects was categorised in to quintiles by quintile value ranges derived from the controls. To assess the risk between cases and controls, an unconditional logistic regression method was used. The model was adjusted for age, social class and total energy intake. To assess for a trend in prostate cancer risk across quintiles of energy and isoflavones intake, chi- squared test for linear trend was performed, considering energy and isoflavones intake as continuous variables.

RESULTS

In the Nottingham-FFQ, there are 131 food items which represent typical foods consumed by British people. We were able to assign isoflavone values to 56 items out of 131. Tofu (coagulated soy milk) contains the highest amount of isoflavone (28062 µg per medium serving size). Overall, the foods that particularly contribute to significant amount of isoflavone intake include peas, beans and fruits (See Table I).

None of the age categories, when compared to baseline category (≤ 50 yrs) showed any significant association with prostate cancer risk and there was no significant trend for increased risk through the age categories.
Table 3 shows that the percentage of cases increased with increased intake of isoflavones compared with controls. The results of the unadjusted model show a clear trend in risk increasing with increased intake of isoflavones (p of trend < 0.05). The findings from the adjusted models suggest that no single quintile of total isoflavone intake was associated with prostate cancer risk, indicated by the inclusion of 1 in the confidence interval.

TABLE I: TOTAL ISOFLAVONES VALUES FOR EACH FOOD

No	Food item	Total isoflavones
1	Beef burger	650.00
2	Sausages	360.00
3	Meat pie	105.90
4	Fish fingers	5.95
5	White bread	87.84
6	Brown bread	157.38
7	Whole meal bread	290.43
8	Cream crackers	4.46
9	Crisp bread, rye	0.25
10	Porridge	1.10
11	Boiled potatoes	0.93
12	Chips	1.65
13	Roast potatoes	1.25
14	Potato salad	1.19
15	White rice	9.75
16	Brown rice	12.60
17	White pasta	7.95
18	Whole meal pasta	6.84
19	Pizza	472.50
20	Low fat yogurt	0.01
21	Full fat yogurt	0.02
22	Pears	0.74
23	Melon	0.36
24	Strawberry	0.16
25	Tin fruit	0.37
26	Dry fruit	12.60
27	Broccoli	0.76
28	Cabbage	0.42

No	Food item	Total isoflavones
29	Peas	2.73
30	Green bean	28.42
31	Mushroom	0.69
32	Bean sprout	240.91
33	Green salad	0.02
34	Sweet corn	0.98
35	Coleslaw	0.10
36	Baked beans	8.52
37	Lentils	3.62
38	Tofu	28062.00
39	Chocolate biscuits	3.83
40	Plain biscuits	2.25
41	Homemade cake	32.89
42	Readymade cake	32.89
43	Homemade buns	142.05
44	Homemade pies	0.95
45	Readymade pies	0.91
46	Homemade pudding	0.14
47	Readymade pudding	0.14
48	Milk pudding	0.45
49	Ice cream	72.09
50	Chocolate bars	3.00
51	Potato crisps	0.69
52	Nuts	6.58
53	Vegetable soup	0.06
54	Tomato ketchup	0.15
55	Jam	0.16
56	Peanut butter	1.86

DISCUSSION

The purpose of this analysis is to explore the potential role of isoflavones in the development of early onset prostate cancer. The dataset used is from the large collection of young prostate cancer cases and age-matched population controls. In this study the mean age at diagnosis for cases was identical i.e. 55.7 years. With age as a categorical variable, there was no significant trend for increased risk through the age categories. The findings of most of the previous studies support increasing age as a strong risk factor for prostate cancer, though it can also occur at a young age [11]. Delongchamps et al, however, stated age as a controversial risk factor, they suggested that it is not age directly that is responsible, but aging probably provided the time necessary for the cumulative effects of environmental exposures and cellular changes essential for the development of a carcinogenic lesion [12].

The median isoflavone intake of cases in this study is 713.7 µg/100mg and of controls is 671.0µg/100mg, about 42.7µg higher in cases compared to controls. Though values were calculated from three main components, only the main frequency table has provided a significant amount of isoflavones. Unlike other dietary components the standard isoflavone daily intake value is not available from the national nutritional survey data, but a recent cohort study in the UK suggested average intake of isoflavones for soy consuming men aged 39-59 years is 854µg/100mg and for non-soy consuming men of the same age is 715µg/100mg. As the controls in our study may or may not necessarily consume soy or soy products regularly, isoflavone intake in the control group is comparable with those in the cohort that are non-soy consumers [13].

The results from the logistic regression model suggest that isoflavones, either as continuous or quintile variables, showed no effect on prostate cancer in the

TABLE II: DISTRIBUTION OF PROSTATE CANCER CASES AND CONTROLS ACCORDING TO AGE

Age as categorical variable	Cases n= 525 (%)	Controls n=843 (%)	OR	95% CI Lower-upper	P value
Age(yrs)*					
≤ 50	48 (9.2)	90 (10.8)	1.00	-	
51-55	166 (31.9)	238 (28.4)	1.31	0.87-1.96	0.91
56-60	306 (58.8)	509 (60.8)	1.13	0.77-1.65	0.54
	missing=5	**missing=6**	P for trend = 0.91		

** Age at diagnosis for cases and age at time of returning questionnaire for controls.*

TABLE III: DISTRIBUTION AND ODDS RATIOS FOR PROSTATE CANCER IN RELATION TO TOTAL ISOFLAVONE INTAKE

Quintile isoflavone intake µg/100mg	Cases (%)	Controls (%)	Unadjusted OR	95% CI Lower-upper	†Adjusted OR	95% CI Lower-upper
<514.81	80 (15.2)	169 (20.0)	1.00	-	1.00	-
514.81- 620.15	92 (17.5)	169 (20.0)	1.15	0.79-1.66	0.98	0.66-1.46
620.15-750.48	109 (20.8)	168 (19.9)	1.37	0.96-1.96	1.15	0.77-1.69
750.48-1066.21	125 (23.8)	169 (20.0)	1.56	1.10-2.22	1.08	0.73-1.61
>1066.21	119 (22.7)	168 (19.9)	1.49	1.05-2.13	1.05	0.69-1.58
	P for trend 0.006					

† Adjusted for age, social class and total energy intake (kcal/day).

doses consumed in the population. Similar finding was reported in a population based case-control study conducted on 433 cases and 483 controls. The study supported no association between isoflavones intake and prostate cancer risk [14].

The evidence of prostate cancer responses to oestrogen therapy together with the evidence from epidemiological studies however, support the lower prostate cancer incidence in countries where phytoestrogen intake is high suggesting the protective effect of phytoestrogens [15].

The findings of this study however, did not support this view and are inconsistent with the results of previous studies. A longitudinal study conducted by Severson et al., on the demographics, diet and prostate cancer among Japanese men living in Hawaii, showed that consumption of tofu ≥ 5 times/week was associated with (65%) risk reduction in prostate cancer compared to those who consumed tofu ≤ 1 times/week [16].

A case-control study in China also supports the idea that consumption of phytoestrogens is inversely related with the risk of prostate cancer [17]. Many other epidemiological studies suggest that there is an inverse relationship between soy intake and the risk of prostate cancer [18-20].

A study conducted by Kolonel et al., 2000, has also shown the protective effect of total legumes/soy food specifically, on prostate cancer risk (OR 0.62 for highest compared to lowest quintile, p for trend 0.06) [21].

The results of this study have found no association between phytoestrogens and prostate cancer risk. The results may be limited by number of factors. The dietary data obtained from the Nottingham-FFQ and further scored for isoflavones. Food listed in Nottingham-FFQ though represents typical food consumed by the British people, few subjects reported having had consumed soy and soy products, foods rich in isoflavones. The average intake of isoflavones in control group is similar to the non-soy consumers reported in Mulligan's study.

A study conducted by Kolonel et al, has shown a protective effect of phytoestrogens and has used a large sample size (1619 cases) [21]. The majority of the previous studies were conducted in settings where the consumption of soy and soy products is very high or they have used modified forms of the FFQ [22].

The main male sex hormone, testosterone, and its active metabolite, dihydrotestosterone (DHT), are essential for the normal growth of the prostate gland and therefore play a role in the development and progression of prostate cancer. The study on the effect of low-isoflavone soy protein isolate (SPI) on reproductive hormones, in healthy young men aged 20-40 years, showed that dihydrotestosterone (DHT) and DHT/ testosterone were significantly reduced by SPI [23].

CONCLUSIONS

This analysis of early onset prostate cancer data was carried out to explore the potential role of isoflavones in prostate cancer risk. The findings supported no association between isoflavone intake and early onset of prostate cancer risk whilst previous studies showed the potential role of this chemical compound.

Keeping in view the results of this study together with difference of results across studies, this could be explained by the methodological differences, different study settings and designs, different instruments used to collect the data on food consumption and the different scales used , such as using tertiles, quartiles and quintiles etc. This very important chemical compound could be detected by adding questions to the Nottingham-FFQ to capture all foods rich in phytoestrogens.

RECOMMENDATION

This kind of large scale, analytical studies should be conducted in Pakistan. These studies can capture several exposures on chronic non-communicable diseases, which are now one of the biggest public health problems of this country along with highly prevalent infectious diseases.

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