Influence of Isoflavone Intake and Equol-producing Intestinal Flora on Prostate Cancer Risk

Yukiko Sugiyama1*, Naoya Masumori2, Fumimasa Fukuta2, Akihiro Yoneta3, Tokimasa Hida3, Toshiharu Yamashita3, Machiko Minatoya1, Yoshie Nagata1, Mitsuru Mori1, Hirokazu Tsuji4, Hideyuki Akaza5, Taiji Tsukamoto2

Abstract

Background: The age-adjusted incidence rate of prostate cancer (PCa) has been reported to be lower among Asians than Western populations. A traditional Japanese meal, high in soybean products or isoflavones, may be associated with a decreased risk of PCa. Equol, which is converted from daidzein by human intestinal flora, is biologically more active than any other isoflavone aglycone. Materials and Methods: We reviewed not only recent epidemiological studies on association of isoflavones with PCa risk, but also recent research on human intestinal bacteria responsible for converting daidzein into equol. Studies were systematically searched from the database published within the last 5 years of from 2008-2012. Results: Five out of 6 articles showed significant association of isoflavones with a decreased risk of PCa, and two of them consistently showed that equol-producers carry a significantly reduced risk of PCa. Furthermore, 5 human intestinal bacteria that can convert daidzein into equol were identified in the last 5 years. Conclusions: If equol can reduce risk of PCa, a possible strategy for reducing the risk of PCa may be to increase the proportion of equol-producers by changing the intestinal flora to carrying an equol-producing bacterium with dietary alteration or probiotic technology.

Keywords: Prostate cancer - isoflavones - equol - soybean products - intestinal flora

Introduction

The age-adjusted incidence rate of prostate cancer (PCa) has been reported to be lower among Asian populations than among Western populations (Curado et al., 2007). Environmental and/or host factors may contribute to this difference in rates. A considerable number of articles have been published assessing dietary habits in association with PCa risk (World Cancer Research Fund/American Institute for Cancer Research, 2007). We previously reviewed them, focusing on the possibility that the traditional Japanese diet may be associated with a decreased risk of PCa (Mori et al., 2009). A traditional Japanese meal consists of a main dish of rice with additional dishes high in soybean products, fish, and other seafood, as well as low in red meat. Isoflavones, polyunsaturated long chain (n-3) fatty acids, and saturated fatty acids were thought to be micronutrients in biological etiology relevant to soybean products, fish, and red meat, respectively (Mori et al., 2009).

The most abundant isoflavones are daidzein and genistein, which together comprise 0.1-0.3 mg/g soybean (Kim et al., 2008), while glycitein is less abundant. Recent researches show that equol, which is converted from daidzein by human intestinal flora, is biologically more active than any other isoflavone (Yuan et al, 2007; Kim et al., 2008; Setchell and Clerici, 2010). A number of bacteria in intestinal flora have also been reported to be responsible for this conversion (Setchell and Clerici, 2010). If a person could make equol in response to consuming soy isoflavones, they are classified as an equol-producer, and the health benefits of soy-based diets may be greater in equol-producers than in equol-nonproducers. However, equol production by a specific human intestinal bacterium has been yet been epidemiological evaluated with regard to risk of PCa.

Accordingly, we began a case-control study on PCa to elucidate the role of equol and a specific human intestinal bacterium, Slackia sp. NATTS (Tsuji et al., 2010), which converts daidzein into equol, supported by a grant from Japanese Government. We have collected data of serum isoflavones concentration, NATTS identification in faeces, and semi-quantitative frequency of food intake, from both PCa cases and their controls. In this article, we reviewed

1Department of Public Health, 2Department of Urology, 3Department of Dermatology, Sapporo Medical University School of Medicine, 4Yakult Central Institute for Microbiological Research, 5Research Center for Advanced Science and Technology, Tokyo University, Tokyo, Japan *For correspondence: ysugi@sapmed.ac.jp
not only recent epidemiological studies on association of isoflavones with PCa risk, but also recent researches on human intestinal bacteria responsible for converting daidzein into equol.

**Analytical Epidemiology**

Analytical epidemiological studies on the risk of PCa, such as cohort and case-control studies, were identified using the MEDLINE database of the National Library of Medicine, United States. Only studies in English from the database published within the last 5 years of from 2008-2012 were included, because our previous review included publications from 1998-2007 (Mori et al.,2009). The keywords “soybean products,” “isoflavones,” “equol,” and “intestinal flora” were added for the search. The statistical significance was set at a 0.05 level. Odds ratios (ORs) and their 95% confidence intervals (95%CI) were cited if shown in the article. Furthermore, we searched recent researches on human intestinal bacteria responsible for converting daidzein into equol.

**Discussion**

As shown in Table 1, 6 articles were found by the search. Miyanaga et al. (2012) reported a randomized, double-blind placebo-controlled trial of oral isoflavones (60 mg/day) for 12 months. The isoflavone tablet included daidzein, genistein, and glycitein. Of the 89 patients evaluated by central pathological review, the incidence of high-grade prostatic intraepithelial neoplasia (HG-PIN) showed no difference between the isoflavone and placebo groups. However, for the 53 patients aged 65 years or more, the incidence of HG-PIN in the isoflavone group was higher than in the placebo group (28.0% vs. 57.1%, P=0.031). They concluded that this result may support the role of isoflavones for prostate cancer risk reduction.

Jackson et al. (2010) evaluated the relationship of spot urinary concentrations of isoflavones with PCs in a hospital-based case-control study in Jamaica, collecting urine samples from 175 cases and 194 controls. As a result, compared with the lowest tertile (non producers of equol), men with the highest tertile of equol concentration in urine showed a decreased risk of total PCs (OR, 0.48; 95%CI, 0.26-0.87) and high-grade PCs (OR, 0.29; 95%CI, 0.13-0.60). They concluded that producers of equol may have a reduced risk of PCa.

Park et al. (2009) reported results from a nested case-control study of the Multiethnic Cohort in Hawaii and California in USA, measuring urine samples of 249 incident cases and 404 controls matched for age, race/ethnicity, and so on. Urinary concentration of daidzein was inversely associated with risk of PCs (OR of the highest quintile vs. the lowest, 0.55; 95%CI, 0.31-0.98). They suggested that high intake of isoflavones, as reflected by urinary excretion of daidzein, may be protective against PCa.

Travis et al. (2009) examined plasma concentration of phyto-estrogens in relation to risk of PCa in a case-control study nested in the European Prospective Investigation into Cancer and Nutrition. Concentrations of genistein, daidzein and equol were measured in plasma samples for

**Table 1. Summary of Studies Assessing the Influence of Isoflavones on Risk of Prostate Cancer During 2008-2012**

<table>
<thead>
<tr>
<th>First author, Country, Study design</th>
<th>Case (or Interventions)</th>
<th>Control (or Cohort)</th>
<th>Duration of follow-up (years)</th>
<th>Items</th>
<th>Contents</th>
<th>Odds ratio</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miyanaga et al., 2012 Japan</td>
<td>Intervention study</td>
<td>42 (Isoflavone)</td>
<td>47 (Placebo)</td>
<td>1</td>
<td>High-grade prostatic intraepithelial neoplasia Age≥65years isoflavones placebo 2/17 (11.8%) 0/19 (0.0%)</td>
<td>0.220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jackson et al., 2010 Jamaica</td>
<td>Case-control study</td>
<td>175</td>
<td>194</td>
<td>Not applicable</td>
<td>genistein daidzein equol Total cancer highest tertile (vs. lowest) 1.23 0.67-2.56 0.502</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Park et al., 2009 USA (Hawaii and California)</td>
<td>Nested case-control study</td>
<td>249</td>
<td>404</td>
<td>1.9</td>
<td>genistein daidzein equol highest tertile (vs. lowest) 0.48 0.26-0.87 0.020</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Travis et al., 2009 Europe</td>
<td>Nested case-control study</td>
<td>950</td>
<td>1,042</td>
<td>15.1</td>
<td>genistein daidzein equol highest tertile (vs. lowest) 0.85 0.47-1.54 0.600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurahashi et al., 2008 Japan</td>
<td>Nested case-control study</td>
<td>201</td>
<td>402</td>
<td>12.8</td>
<td>genistein daidzein equol highest tertile (vs. lowest) 0.72 0.40-1.31 0.318</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Park et al., 2008 USA (Hawaii and Los Angeles)</td>
<td>Cohort study</td>
<td>4,404</td>
<td>82,483</td>
<td>8</td>
<td>genistein daidzein equol highest tertile (vs. lowest) 0.94 0.48-1.92 0.44</td>
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</tbody>
</table>

*95% confidence interval
Table 2. List of Identified Intestinal Bacteria Converting Daidzein to Equol During 2008-2012

<table>
<thead>
<tr>
<th>First author, reference, and publication year</th>
<th>Country</th>
<th>Bacterium strain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsuji et al., 2010</td>
<td>Japan</td>
<td>Slackia sp. NATTS</td>
</tr>
<tr>
<td>Jin et al., 2010</td>
<td>Japan</td>
<td>Slackia equolifaciens sp.</td>
</tr>
<tr>
<td>Matthies et al., 2009</td>
<td>Germany</td>
<td>Slackia sp. HE8</td>
</tr>
<tr>
<td>Maruo et al., 2008</td>
<td>Japan</td>
<td>Adlercreutzia equolifaciens</td>
</tr>
<tr>
<td>Yokoyama and Suzuki, 2008</td>
<td>Japan</td>
<td>Eggerthella sp. YY7918</td>
</tr>
</tbody>
</table>

*Classification, Coriobacteraceae

950 cases and 1,042 matched control participants. As a result, higher concentrations of genistein were associated with lower risk of PCa (OR of the highest quintile vs. the lowest, 0.71; 95%CI, 0.53-0.96). They suggested that a higher intake of isoflavones, as reflected by higher concentration of circulating genistein, may reduce the risk of PCa.

Kurahashi et al. (2008) conducted a nested case-control study within the Japan Public Health Center-based Prospective Study. A total of 14,203 men aged 40-69 years who provided blood samples were followed-up from 1990-2005. After a mean of 12.8 years of follow-up, 201 newly diagnosed PCa and two matched controls for each case were analyzed. As a result, the highest tertile of plasma equol was associated with a decreased risk of total PCa (OR, 0.60; 95%CI, 0.36-0.99). They concluded that isoflavones, especially equol, may prevent the development of PCa.

Park et al. (2008) investigated the relationship of isoflavone intake to PCa risk in a nested case-control study within the Multiethnic Cohort Study in Hawaii and Los Angeles. The analyses included 82,483 men who completed a detailed quantitative food frequency questionnaire from 1993-1996. A total of 4,404 PCa cases were recorded during the average follow-up period of 8 years. As a result of this cohort study, the highest quintile of total isoflavone intake, as well as specific isoflavones, were not associated with risk of PCa, although they slightly reduced risk (OR of total isoflavone, 0.93; 95%CI 0.83-1.04). They concluded that isoflavones may not be significant contributors to reduction of PCa risk in this cohort. As they suggested, it might be thought that levels of soybean or isoflavone consumption in their cohort were too low to detect a protective effect against PCa.

In summary, 5 out of 6 cited articles (Kurahashi et al., 2008; Park et al., 2009; Travis et al., 2009; Jackson et al., 2010; Miyanaga et al., 2012) showed significant association of isoflavones with a decreased risk of PCa, and 2 articles (Kurahashi et al., 2008; Jackson et al., 2010) among them consistently showed that equol-producers carry a significantly reduced risk of PCa.

Breinholt and Larsen (1998) found in 1998 for the first time that equol has more potent estrogenic activity than other flavonoids. Moreover, Lund and his co-workers also isolated an equol-producing bacterium from human faeces, strain NATTS, which was characterized as Gram-positive, non-spor-forming, and rod-shaped. They proposed a novel species of the genus Slackia, NATTS. Tsuji et al. (2012) also showed 3 enzymes and their corresponding genes in conversion of daidzein into equol in the bacterium of the Slackia sp. NATTS. Jin et al. (2010) isolated an equol-producing bacterium, strain DTE, from human faeces, which was characterized as Gram-positive, obligately anaerobic, non-spor-forming, asaccharolytic and rod-shaped. They proposed a novel species of the genus Slackia, Slackia equolifaciens sp. nov.

Matthies et al. (2009) isolated an equol-producing bacterium from human faeces, strain HE8, which was characterized as rod-shaped, Gram-positive, and anaerobic. They proposed a novel species of the genus Slackia, Slackia isoflavoniconvertens. Maruo et al. (2008) isolated an equol-producing bacterium from human faeces, which was characterized as asaccharolytic, obligately anaerobic, non-spor-forming, non-motile, and Gram-positive cocacobacilli. They proposed a novel species of the genus Adlercreutzia, Adlercreutzia equolifaciens sp. nov. Yokoyama et al. (2008) isolated an equol-producing bacterium from human faeces, strain YY7918, which was characterized as non-sporulating, non-motile, and Gram-positive. They proposed a novel species of the genus Eggerthella, Eggerthella sp. YY7918.

In summary, 5 human intestinal bacteria that can convert daidzein into equol were identified in the last 5 years. As these intestinal bacteria need to be epidemiologically evaluated with regard to PCa risk, we began a case-control study including NATTS identification in faeces, as previously mentioned.

Concluding Remarks

Although the incidence rate of PCa is low among Japanese men, it has been increasing, probably because of changes in their dietary habits. If isoflavones, especially equol, can reduce risk of PCa, a possible strategy for reducing risk of PCa may be to increase the proportion of equol-producers by changing intestinal flora to carrying an equol-producing bacterium with dietary alteration or probiotic technology.

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References


