Review

Traditional Japanese diet and prostate cancer

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The traditional Japanese diet has been suggested by some researchers to be associated with a decreased risk of prostate cancer (PCa). In this paper, we assumed the following three characteristics of the traditional Japanese diet high in soybean products, high in fish, and 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. Analytical epidemiological studies on the risk of PCa were identified using the MEDLINE database from 1998 to 2007. Some published studies showed a negative association of soybean products and isoflavones to PCa risk, an inverse association for fish or polyunsaturated long chain ($n-3$) fatty acids such as eicosapentaenic acid (EPA) and docosahexaenoic acid (DHA) with PCa risk, and a positive association of red meat or saturated fatty acids with PCa risk, respectively. In conclusion, although it is possible that the traditional Japanese diet may reduce the risk of PCa through a combination of characteristics such as being high in soybean products, high in fish, and low in red meat, further well-designed epidemiological studies such as nested case-control studies with nutritional analyses of blood samples are needed to confirm this association.

Keywords: Fish / Isoflavones / Prostate cancer / Red meat / Soybean products

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1 Introduction

The age-adjusted incidence rate of prostate cancer (PCa) has been reported to be lower among Asian populations than among Western populations [1]. Environmental and/or host factors may contribute to this difference in rates. The age-adjusted incidence of PCa among Japanese migrants to Hawaii or California has been shown to be much higher than that among Japanese people in Japan and to be close to that among Caucasians [1]. The as yet established risk factors for PCa are aging and having a family history of the disease. African Americans have been shown to carry the highest incidence of PCa, as compared to other races [1]. However, it is still unclear whether this difference is due to genetic or environmental factors.

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Abbreviations: DHA, docosahexaenoic acid; **EPA,** eicosapentaenic acid; **CI,** confidence interval; **PCa,** prostate cancer; **RR,** risk ratio

The most probable of all other possible factors may be dietary habits [2]. A considerable number of studies have been published assessing dietary habits in association with PCa risk. We reviewed these, focusing on the possibility that the traditional Japanese diet may be associated with a decreased risk of PCa. 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. We defined the traditional Japanese diet as consisting of three important characteristics (high in soybean products, high in fish, and low in red meat) because these components have already been assessed with regard to the risk of PCa not only in the West but also in the East [2–4].

Although there are other popular Japanese foods and beverages, such as rice, noodles (udon, soba, somen), pickles, seaweed, and green tea, no extensive studies on these foods have yet been undertaken or reported. As reviewed by Siddiqui *et al*. [5], very few studies have been conducted to evaluate the effect of green tea consumption on human PCa. Although lean body stature resulting from low energy intake may also be more common among the Japanese, only a few reports on the association between BMI and PCa risk have been published in the East, as reviewed by MacInnis and English [6].

Several methodological limitations may have affected the results from previous studies on the relationship between dietary habits and PCa risk. First, misclassifications of dietary intake may have occurred, amounting to measurement errors on dietary questionnaires. Additionally, differential recall bias also exists in case-control studies, because cancer cases may recall their dietary habits differently than the controls. If controls were selected from patients with the disease, selection bias may have occurred in case-control studies. Furthermore, nonresponding subjects may have influenced some of the results. The long latent period of cancer also makes the effects of dietary factors ambiguous and hard to isolate. Finally, the intake of a single nutrient may be affected by the intake of all other nutrients; it is difficult to highlight only a specific nutrient or subgroup of nutrients with respect to PCa risk, even if statistical adjustments are used. We have pointed out the limitations of the studies cited in the text, if they contain any other biases.

2 Methods

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 most recent 10 years (1998 – 2007) were included. The keywords "soybean products," "fish," and "red meat" were used for the search. The other keywords "isoflavones", "eicosapentaenic acid (EPA), or docosahexaenoic acid (DHA)", and "saturated fatty acids" were also used for the search, as the relevant micronutrients of soybean products, fish, and red meat, respectively. We describe the results of the published articles regarding the effects of each of these three food items in the order in which they are named here. The statistical significance was set at 0.05 level.

Soybean products and fish contain other micronutrients, such as polyunsaturated ($n - 6$) fatty acids (soybean products), vitamin D (fish) and retinol (fish), which possibly modify the risk of PCa. However, we did not focus on these micronutrients because they have been less extensively assessed. We have cited two epidemiological studies on the ingestion of well-done red meat, since the carcinogenic chemicals produced during their preparation have been studied thoroughly.

In Japan, soybeans are ingested mainly in the form of tofu (soybean curd), natto (fermented soybean), and miso (slowly fermented soybean). Tonyu (soymilk), aburage (fried soybean curd), edamame (green soybeans), and other soybean products are also consumed, though in smaller amounts. However, all soybean products, even those not consumed in Japan, were included in this review.

3 Results and discussion

3.1 Diets high in soybean products

As shown in Table 1, 12 articles assessed soybean products among food items and 6 assessed isoflavones as relevant micronutrients, with regard to the risk of PCa [7 – 21]. Isoflavones, which are classified as phytoestrogens found mainly in soybeans and soy products, possess not only antioxidant properties but also weak estrogenic activity. They compete with erstadiol in binding to the nuclear estrogen receptor and also stimulate the synthesis of sex hormone-binding globulin, which may result in the reduction of PCa risk [3]. In addition, isoflavones can inhibit tyrosine-specific protein kinase, DNA topoisomerase, and steroid-metabolizing enzymes, including 5α-reductase and aromatase. Isoflavones can also inhibit angiogenesis. These inhibitions contribute to protection against carcinogenesis of the prostate [3].

Heald *et al*. [7] reported based on a case-control study of 433 cases and 483 controls with benign prostate hyperplasia in Scotland that the consumption of soy-based food products had a significant protective effect against PCa. However, they also reported using a nonfasting blood sample that the serum concentrations of isoflavone aglycones such as genistein, daizein, and equol, a type of isoflavone aglycone, were not associated with PCa risk. Because blood samples were obtained after the disease was diagnosed, a dietary modification bias, including isoflavone product consumption, might have existed. Chen *et al*. [9] showed based on a case-control study of 237 cases and 481 hospital controls in Taiwan that frequent consumption of folk vegetarian foods consisting mainly of tofu (soybean curds) and other soybean products was significantly associated with a reduced risk of PCa. Because they used binary analysis, they were unable to assess a dose-response relationship.

Sonoda *et al*. [10] indicated based on a case-control study of 140 cases and 140 hospital controls in Japan that an increased intake of natto (fermented soybeans) was negatively associated with PCa risk at a marginally significant level. However, they found that the association of soybean products as a whole with PC risk was insignificant. Lee *et al*. [14] denoted based on a case-control study of 133 cases and 265 population controls in China that larger intake of tofu or combined soy foods was significantly associated with decreased risk of PCa. They also showed that an increased intake of genistein was significantly negatively related to the risk of PCa. Kolonel *et al*. [15] reported based on a case-control study of 1619 cases and 1618 population controls in the United States that increased soyfood consumption was significantly inversely associated with the risk of PCa. A relatively low response rate among the controls (58%) was a limitation of this study.

Jacobson *et al*. [18] demonstrated based on a 16-year follow-up study of 12 365 Seventh-day Adventist men result-

Table 1. Summary of studies assessed the influence of soybean products or isoflavones on risk of PCa

First author	Year[a)]	Ref.[b)]	Country	Design of study	Cases	Controls	Cohort (Follow-up)	Variable	Category	RR[c)]	95% CI[d)]
Soybean products as food items											
Heald	2007	7	Scotland	Case-control	433	483	–	Soy food	Yes *vs.* no	0.52	0.30, 0.91
Kurahashi	2007	8	Japan	Prospective	307	–	43 509 (9 years)	Miso (soybean paste) soup	≧356.0 mL/day (*vs.* <110.0 μL/day)	1.04	0.72, 1.50
								All soy food	≧107.4 g/day (*vs.* <46.6 g/day)	0.82	0.57, 1.19
Chen	2005	9	Taiwan	Case-control	237	481	–	Vegetarian food including soybean products	≧Moderate (*vs.* less or none)	0.66	0.48, 0.91
Sonoda	2004	10	Japan	Case-control	140	140		Tofu (soybean curd)	≧96.4 g/day (*vs.* <19.7 g/day)	0.47	0.20, 1.08
								Natto (fermented soybeans)	≧40.0 g/day (*vs.* <5.7 g/day)	0.25	0.05, 1.24
								All soy products	≧187.2 g/day (*vs.* <77.0 g/day)	0.53	0.24, 1.14
Nomura	2004	11	United States	Prospective	304		5 877 (23 years)	Tofu	>240 g/wk (vs. 0 g/wk)	0.82	0.54, 1.23
Allen	2004	12	Japan	Prospective	196		18 115 (34 years)	Tofu	Almost daily (*vs.* <twice/wk)	0.88	0.58, 1.35
								Miso soup	Almost daily (*vs.* <twice/wk)	0.94	0.67, 1.33
								Total soy	High (*vs.* low)	0.79	0.53, 1.18
Jian	2004	13	China	Case-control	130	270		Fermented soy products	>4.00 g/day (*vs.* 0 g/day)	2.02	1.08, 3.78
Lee	2003	14	China	Case-control	133	265		Tofu	>34.5 g/day (*vs.* <14.3 g/day)	0.58	0.35, 0.96
								Combined soy foods	>111.8 g/day (*vs.* <27.5 g/day)	0.51	0.28, 0.95
Kolonel	2000	15	United States	Case-control	1 619	1618		Soy food	>39.4 g/day (*vs.* 0 g/day)	0.62	0.44, 0.89
Sung	1999	16	Taiwan	Case-control	90	180		Soy milk	Yes (*vs.* no)	0.95	0.45, 2.00
Villeneuve	1999	17	Canada	Case-control	1 623	1623		Tofu or soybean	Some (*vs.* none)	0.8	0.6, 1.1
Jacobson	1998	18	United States	Prospective	225		12 395 (16 years)	Soy milk	>once/day (*vs.* never)	0.3	0.1, 0.9
Isoflavones as micronutrients											
Heald	2007	7	Scotland	Case-control	433	483		Isoflavone	>1982.8 μg/day (*vs.* <581.1 μg/day)	1.18	0.79, 1.75
								Genistein (serum)	>64.53 nmol/L (*vs.* <14.23 nmol/L)	1.36	0.76, 2.43
								Daizein (serum)	>33.69 nmol/L (*vs.* <8.48 nmol/L)	1.34	(0.75, 2.40)
								Equal (serum)	>0.10 nmol/L (*vs.* 0.0 nmol/L)	1.07	1.07, 1.61
Kurahashi	2007	8	Japan	Prospective	307		43 509 (9 years)	Genistein	≧32.8 mg/day (*vs.* <13.2 mg/day)	0.71	0.48, 1.03
								Daizein	≧20.4 mg/day (*vs.* <8.5 mg/day)	0.77	0.52, 1.13
Nagata	2007	19	Japan	Case-control	200	200		Isoflavone	>89.9 mg/day (*vs.* <30.5 mg/day)	0.48	0.25, 0.93
								Genistein	>2.5 mg/day (*vs.* <1.1 mg/day)	0.68	0.39, 1.20
								Daizein	>1.9 mg/day (*vs.* <0.8 mg/day)	0.64	0.36, 1.17
Ozasa	2004	20	Japan	Prospective (nested case-control)	52	113	48 019 (12 years)	Genistein (serum)	>682 nmol/L (*vs.* <239 nmol/L)	0.76	0.32, 1.82
								Daizein (serum)	>239 nmol/L (*vs.* <89 nmol/L)	0.74	0.31, 1.76
								Equol (serum)	>56.1 nmol/L (*vs.* <1.9 nmol/L)	0.39	0.15, 0.98

Table 1. Continued

First author	Year[a]	Ref.[b]	Country	Design of study	Cases	Controls	Cohort (Follow-up)	Variable	Category	RR[c]	95% CI[d]
Lee	2003	14	China	Case-control	133	265		Genistein	>62.0 mg/day (*vs.* <17.9 mg/day)	0.51	0.29, 0.97
								Daizein	>36.3 mg/day (*vs.* <10.0 mg/day)	0.56	0.31, 1.04
Strom	1999	21	United States	Case-control	83	107		Genistein	>29.7 μg/day (*vs.* ≧29.7 μg/day)	0.71	0.39, 1.30
								Daizein	>22.8 μg/day (*vs.* ≧22.8 μg/day)	0.57	0.31, 1.05

a) Year of publication.
b) Reference number.
c) Risk ratio (RR).
d) 95% confidence interval.

ing in 225 cases in the United States that the frequent consumption of soymilk, a beverage containing isoflavones, was associated with a reduction in PCa risk. The lack of information about the portion sizes of soymilk might have made it impossible to evaluate isoflavone intake quantitatively. Nagata *et al*. [19] showed based on a case-control study of 200 cases and 200 hospital controls in Japan that isoflavones were significantly associated with a decreased risk of PCa. Ozasa *et al*. [20] reported based on a nested case-control study of 52 cases and 113 controls in a 12-year follow-up study of 43 509 Japanese people that serum equol, a metabolite of daizein, detected in stocked sera were significantly inversely associated with the risk of PCa. Conversely, a case-control study of 130 cases and 270 hospital controls in China conducted by Jian *et al*. [13] indicated a significant positive association between fermented soy products and PCa risk. Because the controls were inpatients with various diseases, selection bias might have affected the study results.

In summary, 6 out of 12 published articles showed a significant negative relationship between soybean product consumption and PCa risk, while 1 out of 12 showed a significant positive relationship. Additionally, 3 out of 12 published articles showed a significant inverse relationship between isoflavone consumption and PCa risk. The mean daily intake levels of isoflavones were shown to be lower (<3 mg) in Western populations than in East Asian populations (47.2 mg) [14]. The various significance level results may in part reflect this difference between the study subject groups.

3.2 Diets high in fish

As shown in Table 2, 13 articles assessed the intake of fish with regard to PCa risk, while 9 assessed EPA and DHA in the same capacity as relevant micronutrients [9, 10, 12, 17, 18, 22–37]. Fish contains abundant polyunsaturated long-chain ($n-3$) fatty acids such as EPA and DHA which may be related to the mechanism for the protective effect of fish against PCa. Studies of animal models and on cell lines from human prostate tumors have shown that these fatty acids suppress tumor cell growth, probably through the inhibition of eicosanoid biosynthesis, since eicosanoids have been shown to be related to tumor development [4]. Another possibility is that EPA and DHA have numerous anti-inflammatory properties that have been linked with decreased PCa risk [31]. However, alternative or additional potential protective agents in fish such as vitamin D or retinol, should not be ruled out.

Terry *et al*. [25] reported based on a 30-year follow-up study of 6292 male twins resulting in 466 cases in Sweden that men who never or seldom consumed fish were significantly more at risk of PCa. The strength of this study was that it included a population-based cohort study and dietary assessment before disease occurrence. Jain *et al*. [28] showed based on a case-control study of 617 cases and 636 controls in Canada that greater consumption of fish was significantly inversely associated with PCa risk. Chavarro *et al*. [30] indicated based on a nested case-control study of 476 cases and 476 controls in a 13-year follow-up study of 14 916 men, the Physician's health study, in the United Sates that higher blood levels of EPA and DHA were significantly related to decreased PCa risk. The strength of this study was that blood samples were collected before PCa diagnosis.

Leitzmann *et al*. [31] denoted based on a 14-year follow-up study of 47 866 men resulting in 2965 cases in the United States that EPA and DHA intakes were marginally significantly related to reduced PCa risk. Norrish *et al*. [36] demonstrated based on a case-control study in New Zealand the presence of a significant inverse association between EPA and DHA levels in erythrocytes and PCa risk. Conversely, Allen *et al*. [12] showed based on a 34-year follow-up study of 18 115 men resulting in 196 cases of atomic bomb survivors in Hiroshima and Nagasaki, Japan, that fish intake was significantly positively associated with PCa risk. However,

Table 2. Summary of studies assessed the influence of fish, EPA, or DHA on risk of PCa

First author	Year[a]	Ref.[b]	Country	Design of study	Cases	Controls	Cohort (Follow-up)	Variable	Category	RR[c]	95% CI[d]
Fish as food items											
Park	2007	22	United States	Prospective	4404		82 483 (8 years)	Fish	Highest quintile (*vs.* lowest)	1.04	0.93, 1.15
Rohrmann	2007	23	United States	Prospective	199		3892 (15 years)	Fish	≧5 Times/wk (*vs.* ≦ once/wk)	0.86	0.44, 1.67
Chen	2005	9	Taiwan	Case-control	237	481		Fish/shellfish	≧Moderate (*vs.* little or none)	1.12	0.80, 1.56
Sonoda	2004	10	Japan	Case-control	140	140		Fish	≧130.7 g/day (*vs.* <47.3 g/day)	0.45	0.20, 1.02
Allen	2004	12	Japan	Prospective	196		18 115 (34 years)	Fish	Almost daily (*vs.* <twice/wk)	1.54	1.03, 2.31
Augustsson	2003	24	United States	Prospective	2482		47 882 (12 years)	Fish	>3 Times/wk (*vs.* <twice/mo)	0.93	0.80, 1.08
Terry	2001	25	Sweden	Prospective	466		6292 (30 years)	Fish	Never or seldom (*vs.* moderate)[e]	2.3	1.2, 4.5
Schuurmann	1999	26	Netherlands	Prospective	642		58 279 (6.3 years)	Fish	>20 g/day *vs.* 0 g/day)	1.03	0.80, 1.34
Sung	1999	16	Taiwan	Case-control	90	180		Fish	>once/wk (*vs.* ≦once/wk)	1.09	0.61, 1.96
Villenuve	1999	17	Canada	Case-control	1623	1623		Fish	≧4 times/wk (*vs.* none)	1.0	0.7, 1.3
Deneo-pellegrini	1999	27	Uruguay	Case-control	175	233		Fish	Highest quartile *vs.* lowest	0.9	0.5, 1.8
Jain	1999	28	Canada	Case-control	617	636		Fish	>45.1 g/day (*vs.* 9.5 g/day)	0.66	0.50, 0.89
Fernandez	1999	29	Italy	Case-control	127	7990		Fish	≧twice/wk (*vs.* ≦once/wk)	0.7	0.4, 1.1
EPA or DHA as micronutrients											
Park	2007	22	United States	Prospective	4404		82 483 (8 years)	EPA[f]	Highest quintile (*vs.* lowest)	1.01	0.91, 1.13
								DHA[g]	Highest quintile (*vs.* lowest)	0.99	0.89, 1.09
Chavarro	2007	30	United States	Prospective (Nested case-control)	476	476	14 916 (13 years)	EPA (blood)	Highest quintile (*vs.* lowest)	0.57	0.36, 0.92
								DHA (blood)	Highest quintile (*vs.* lowest)	0.60	0.39, 0.93
Leitzmann	2004	31	United States	Prospective	2965		47 866 (14 years)	EPA	>0.066% of energy (*vs.* <0.014%)	0.88	0.76, 1.01
								DHA	>0.122% of energy (*vs.* <0.023%)	0.89	0.78, 1.04
Hodge	2004	32	Australia	Case-control	858	905		EPA	>0.142 g/day (*vs.* ≦0.077 g/day)	0.8	0.6, 1.1
								DHA	>0.25 g/day (*vs.* ≦0.14 g/day)	1.0	0.7, 1.4
Männisto	2003	33	Finland	Prospective (nested case-control)	246	246	29 133 (8 years)	EPA (serum)	Highest quartile (*vs.* lowest)	1.12	0.61, 2.04
								DHA (serum)	Highest quartile (*vs.* lowest)	0.71	0.40, 1.26
Kristal	2002	34	United States	Case-control	605	592		EPA + DHA (local)	>0.24 g/day (*vs.* <0.03 g/day)	1.05	0.68, 1.63
								EPA + DHA (regional or distant)	>0.24 g/day (*vs.* <0.03 g/day)	0.84	0.44, 1.58
Newcomer	2001	35	United States	Case-control	67	156		EPA (erythorcyte membrane)	≧0.68% Of relative weight (*vs.* <0.39%)	1.3	0.6, 3.0
								DHA (erythorcyte membrane)	≧4.86% Of relative weight (*vs.* <3.26%)	1.0	0.4, 2.3
Norrish	1999	36	New Zealand	Case-control	317	480		EPA (erythorcyte)	Highest quartile (*vs.* lowest)	0.59	0.37, 0.95

Table 2. Continued

First author	Year[a]	Ref.[b]	Country	Design of study	Cases	Controls	Cohort (Follow-up)	Variable	Category	RR[c]	95% CI[d]
								DHA (erythorcyte)	Highest quartile (*vs.* lowest)	0.62	0.39, 0.98
Schuurmann	1999	37	Netherlands	Prospective	642		58 279 (6.3 years)	EPA	Highest quintile (*vs.* lowest)	1.00	0.73, 1.35
								DHA	Highest quintile (*vs.* lowest)	1.03	0.75, 1.40

a) Year of publication.
b) Reference number.
c) Risk ratio.
d) 95% confidence interval.
e) Moderate intake was reference category.
f) Eicosapentaenic acid.
g) Docosahexaenoic acid.

a major disadvantage of this study was that each questionnaire covered only a limited number of foods, portion size was not recorded, and the reported results could not be adjusted for total energy intake.

In summary, 2 out of 13 reviewed articles revealed a significantly negative relationship between fish consumption and PCa risk, while 1 out of 13 showed a significantly positive relationship. Additionally, 2 out of 9 reviewed articles revealed a significantly inverse relationship between EPA/DHA consumption and PCa risk.

3.3 Diets low in red meat

If a diet high in red meat is associated with PCa risk, it is possible that the traditional Japanese diet's being low in red meat may protect against PCa development. As shown in Table 3, 19 articles assessed red meat with regard to PCa risk, and 10 assessed saturated fatty acids or animal fat in the same capacity as relevant micronutrients [9, 10, 12, 16, 17, 22, 23, 26–28, 34, 37–48]. The experimental data suggest that saturated fatty acids from animal red meat might lead to increased testosterone levels and that this might eventually lead to increased cell division, the activation of proto-oncogene genes, and the deactivation of tumor suppressor genes. A high-fat diet with a high ratio of saturated to polyunsaturated fat was shown to increase both total urinary androgens and total plasma testosterone concentration [4].

Rodriguez *et al*. [40] indicated based on an 11-year follow-up study of 65 548 men resulting in 5113 cases in the United States that red meat consumption was significantly associated with higher risk of PCa among black men, though not among white men. Hayes *et al*. [43] reported based on a case-control study of 932 cases and 1201 population controls in the United Sates that increased consumption of either red meat or animal fat was significantly related to an increased risk of PCa among black men, though not among white men. Although it was unclear why red meat intake was associated with an increased risk of PCa in black men, but not white men, red meat may have enhanced the progression of tumors to a clinically detectable level, especially among black men.

Roman *et al*. [46] showed based on a case-control study of 217 cases and 434 controls in Spain that animal fat, but not saturated fat, was significantly positively associated with PCa risk. Because their control group consisted of a combination of population controls and hospital controls, it is difficult to infer the magnitude of selection bias in their study. Lee *et al*. [48] reported based on a case-control study of 133 cases and 265 neighborhood controls in China that an increased intake of saturated fat was significantly positively associated with PCa risk. However, they did not conduct a study in order to evaluate the validity or reliability of their questionnaire.

Other possible causal mechanisms for the effects of a high-red meat diet should not be ignored. For example, a diet high in meat can result in significant exposure to carcinogenic chemicals, such as polycyclic aromatic hydrocarbons, heterocyclic amines, and *N*-nitroso compounds (nitrosamines), that are generated when meats are prepared with such methods as smoking or grilling at high temperatures [4]. Cross *et al*. [41] reported in an 8-year follow-up study of 29 361 men in the United States that a high intake of very well done meat increased the risk of PCa. The strengths of this study included the fact that it collected detailed information on meat and meat cooking practices. However, the mean follow-up period (8 years) was shorter than that of most of the other prospective studies. Norrish *et al*. [44] showed based on a case-control study of 317 cases and 480 population controls in New Zealand that a preference for well-done beefsteak was significantly positively associated with PCa risk. As they mentioned, it was difficult to determine the validity and reliability of the questionnaire with respect to self-reported meat-cooking practices and "doneness."

In summary, 2 out of 19 reviewed articles revealed a significantly positive relationship between red meat consump-

Table 3. Summary of studies assessed the influence of red meat or saturated fatty acids on risk of PCa

First author	Year[a]	Ref.[b]	Country	Design of study	Cases	Controls	Cohort (follow-up)	Variable	Category	RR[c]	95% CI[d]
Red meat as food items											
Neuhouser	2007	38	United States	Prospective	890		12 025 (11 years)	Meat	≧1.3 Servings/day (*vs.* <0.60/day)	0.95	(0.75, 1.20)
Smit	2007	39	Puerto Rico	Prospective	167		9777 (41 years)	Meat	≧5 oz/d (*vs.* 0/day)	1.27	(0.62, 2.63)
Park	2007	22	United States	Prospective	4404		82 483 (8 years)	Red meat	Highest quintile (*vs.* lowest)	0.97	(0.87, 1.07)
Rohrmann	2007	23	United States	Prospective	199		3892 (15 years)	Red meat	>120.64 g/day (*vs.* <70.14 g/day)	0.87	(0.59, 1.32)
Rodriguez	2006	40	United States	Prospective	5113		65 548 (11 years)	Red meat (blacks)	≧657 g/wk (*vs.* <246 g/wk)	2.0	(1.0, 4.2)
								Red meat (whites)	≧657 g/wk *vs.* <246 g/wk)	1.0	(0.9, 1.0)
Chen	2005	9	Taiwan	Case-control	237	481		Pork	≧Moderate (*vs.* little or none)	1.24	(0.84, 1.84)
								Beef	≧Moderate (*vs.* little or none)	1.05	(0.76, 1.46)
Cross	2005	41	United States	Prospective	1338		29 361 (8 years)	Red meat	>146.0 g/day (*vs.* <43.5 g/day)	0.91	(0.73, 1.12)
								Very well-done meat	>10.0 g/day (*vs.* 0 g/day)	1.42	(1.05, 1.92)
Sonoda	2004	10	Japan	Case-control	140	140		Meat	≧62.8 g/day (*vs.* <21.1 g/day)	1.80	(0.81, 3.98)
Leitzmann	2004	31	United States	Prospective	2965		47 866 (14 years)	Beef, pork, or lamb	≧once/day (*vs.* <once/month)	1.58	(0.83, 2.99)
Hodge	2004	32	Australia	Case-control	858	905		Meat	>6.5 times/wk (*vs.* 10.2 times/wk)	1.0	(0.8, 1.4)
Allen	2004	12	Japan	Prospective	196		18 115 (34 years)	Pork	Almost daily (*vs.* <twice/wk)	1.24	(0.61, 2.54)
Michaud	2001	42	United States	Prospective	1897		51 529 (10 years)	Red meat (Stage A)	>116 g/day (*vs.* <28 g/day)	0.91	(0.75, 1.1)
								Red meat (stage C, D, fatal)	>116 g/day (*vs.* <28 g/day)	1.15	(0.80, 1.7)
Schuur-mann	1999	26	Netherlands	Prospective	642		58 279 (6.3 years)	Fresh meat and poultry	>137 g/day (*vs.* <73 g/day)	1.07	(0.77, 1.47)
Hayes	1999	43	United States	Case-control	932	1201		Red meat	Highest quartile (*vs.* lowest)	1.4	trend, $P = 0.04$
Sung	1999	16	Taiwan	Case-control	90	180		Beef	>Once/wk *vs.* (≦once/wk)	1.36	(0.74, 2.60)
Norrish	1999	44	New Zea-land	Case-control	317	480		Well-done beefsteak	Ever (*vs.* never)	1.68	(1.02, 2.77)
Villenuve	1999	17	Canada	Case-control	1623	1623		Meat	≧14 times/wk (*vs.* <3 times/wk)	1.0	(0.7, 1.3)
Deneo-Pel-legrini	1999	27	Uruguay	Case-control	175	233		Red meat	>379 g/wk (*vs.* 182 g/wk)	1.7	(0.8, 3.4)
Jain	1999	28	Canada	Case-control	617	636		Red meat	>55.1 g/day (*vs.* <15.9 g/day)	1.02	(0.77, 1.35)
Saturated fatty acid as micronutrients											
Park	2007	22	United States	Prospective	4404		82 483 (8 years)	Saturated fat	Highest quintile (*vs.* lowest)	0.94	(0.85, 1.04)
Neuhouser	2007	38	United States	Prospective	890		12 025 (11 years)	Saturated fat	≧33.6 g/day (*vs.* 18.3 g/day)	0.98	(0.71, 1.35)
Nagata	2007	19	Japan	Case-control	200	200		Saturated fatty acid	>47.4 g/day (*vs.* <25.1 g/day)	0.89	(0.49 1.62)
Bidoli	2005	45	Italy	Case-control	1294	1451		Saturated fatty acid	Highest quintile (*vs.* lowest)	0.9	(0.7, 1.2)
Kristal	2002	34	United States	Case-control	605	592		Saturated fat (local)	>15.7%cr (*vs.* <9.9%cr)	1.09	(0.69, 1.72)
								Saturated fat (regional or distant)	>15.7%cr (*vs.* <9.9%cr)	1.82	(0.93, 3.56)

Table 3. Continued

First author	Year[a]	Ref.[b]	Country	Design of study	Cases	Controls	Cohort (follow-up)	Variable	Category	RR[c]	95% CI[d]
Ramon	2000	46	Spain	Case-control	217	434		Animal fat	>47.3 g/day (*vs.* <18.6 g/day)	2.00	(1.20, 3.2)
								Saturated fat	>40.5 g/day (*vs.* <16.7 g/day)	0.97	(0.66, 1.40)
Hayes	1999	43	United States	Case-control	932	1201		Animal fat (whites)	≧62 g/day (*vs.* ≦33 g/day)	2.0	(1.2, 3.1)
								Animal fat (blacks)	≧62 g/day (*vs.* ≦33 g/day)	1.1	(0.7, 1.7)
Tzonou	1999	47	Greece	Case-control	320	246		Saturated fat	Increment of 1 SD	1.13	(0.85, 1.50)
Schuurmann	1999	37	Netherlands	Prospective	642		58 279 (6.3 years)	Saturated fatty acid	Highest quintile (*vs.* lowest)	1.19	(0.80, 1.76)
Lee	1998	48	China	Case-control	133	265		Saturated fat	>38.5 g/day (*vs.* <17.7 g/day)	2.92	(1.50, 5.72)

a) Year of publication.
b) Reference number.
c) Risk ratio.
d) 95% confidence interval.

tion and PCa risk, and 2 out of 10 reviewed articles revealed a significantly positive relationship between saturated fatty acid intake and PCa risk. Two articles showed a significantly positive association between the intake of well-done steak and PCa risk. None of the reviewed articles showed the frequent consumption of red meat or saturated fatty acids to be associated with a significantly decreased risk of PCa.

4 Concluding remarks

Nested case-control studies with biochemically analyzed stocked blood samples may be the most desirable method for evaluating the relationship between micronutrients and PCa risk. Only three such reports were published during the most recent 10 years, but two of them produced significant results. Specifically, serum equal (the potent aglycone of isoflavones) level was shown to be significantly inversely associated with PCa risk in a nested case-control study [20]. Likewise, EPA and DHA levels in erythrocytes were demonstrated to be associated with significantly decreased PCa risk in another nested case-control study [36].

In conclusion, although it is possible that the traditional Japanese diet may reduce the risk of PCa through a combination of characteristics, such as a diets high in soybean products, high in fish, and low in red meat, further well-designed epidemiological studies such as nested case-control studies with nutritional analyses of blood samples are needed to confirm this association. Isoflavones, polyunsaturated long-chain ($n-3$) fatty acids, and saturated fatty acids are good candidates for further nutritional analysis in blood samples, due to their potential relevance to PCa risk.

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