RESEARCH COMMUNICATION

Weight Gain and Family History of Prostate or Breast Cancers as Risk Factors for Prostate Cancer: Results of a Case-control Study in Japan

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Abstract

The increase in the incidence rate of prostate cancer may be associated with changes in lifestyle in Japanese men. Accordingly, we conducted a case-control study to assess risk factors. A total of 117 (82.3%) of the 142 prostate cancer patients asked filled out the self-administrated questionnaires which included items about their lifestyle habits over the period of one or two years before their diagnosis. Four controls per case, namely 468, were randomly selected from resident registries with age and address matched with each case, and 318 controls (69.5%) filled out the same questionnaire as the cases. Data for 277 controls were used for the analysis, excluding 41 subjects with a history of previous cancer. The conditional logistic regression model was utilized for analyzing the individually age and address-matched data, and odds ratios (ORs) and their 95% confidence intervals (95%CIs) were calculated for potential risk factors. Higher body mass index at 20 years of age was marginally significantly associated with a decreased risk (P for trend=0.051), and larger weight gain in adult age was significantly associated with an increased risk (P for trend=0.041). History of prostate cancer in fathers or brothers was significantly associated with an increased risk (OR=9.71, 95%CI 3.59, 26.27), and history of breast cancer in mothers or sisters was also significantly associated with an increased risk (OR=2.70, 95%CI 1.12, 6.49). The recent increase in the incidence rate of prostate cancer may possibly be brought about by an increased proportion of Japanese men with large weight gain in adult age.

Keywords: Prostate cancer - case-control study - family history - weight gain - body mass index

Asian Pacific J Cancer Prev, **12**, 743-747

Introduction

Age-adjusted incidence rates of prostate cancer (PCa) have been reported to be lower among Asian populations than among Western populations (Parkin et al., 2002). However, the age-adjusted incidence rate of prostate cancer has increased in Japan, and became as high as 27.3 per 100,000 in 2003 based on data from 13 population-based cancer registries standardized to the World model population (Matsuda et al., 2009). Furthermore, the age-adjusted incidence rates of PCa among Japanese migrants to Hawaii or California have been shown to be much higher than those among Japanese people in Japan, and to be closer to those among Caucasians in Hawaii and California (Parkin et al., 2002).

Environmental and genetic factors have been suggested to be associated with the risk of PCa (Hayes, 2001; Plats and Giovannucci, 2002). History of PCa in first-degree relatives is a well-known risk factor (Stanford, 2001). African Americans have been shown to carry the highest incidence of PCa compared to other races (Parkin et al., 2002). However, it is still unclear whether this difference is due to genetic or environmental factors.

Increased prevalence of obese males has also been reported in Japan. According to the National Survey on Health and Nutrition in Japan, the proportion of men whose body mass index (BMI) was more than or equal to 25.0 aged 40 years to 59 years of age increased from about 25% in 1987 to about 34% in 2007 (Health and Welfare Statistics Association, 2009). Consequently, it is possible that the recent increasing trend of PCa incidence in Japan was brought about by the increased prevalence of obese males in Japan if obesity is associated with risk of PCa. We have suggested that the recent decrease in having a traditional Japanese diet (Mori et al., 2009), especially the decrease in the intake of soybean products (Nagata et al., 2007) in Japanese men, may be associated with the increase in the incidence rate of PCa in Japan. Decrease in the intake of soybean products might be one of the

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most prominent changes in Japanese dietary habits, as we reported the significantly decreased trend of intake of soybean isoflavones in the younger generation (Fujimoto et al., 2008). Therefore, we conducted a case-control study to assess the risk factors of PCa in Hokkaido, Japan, with special reference to dietary habits, obesity and family history of cancer.

Materials and Methods

There were 168 PCa patients who were newly pathologically diagnosed at the Department of Urology, Sapporo Medical University from January, 2007 to April, 2008. We excluded 26 patients from the study because 5 patients died, 19 patients were in too poor health, 1 subject moved out of the Hokkaido Prefecture and 1 subject was not Japanese. Among the residual 142 PCa patients, informed consent was obtained from 117 patients (82.3%).

The self-administrated questionnaire consisted of various inquiries over the period of one or two years before their diagnosis such as followings; frequencies of consumption for 28 foods or beverages such as beef, pork, ham, sausages, soybean products, vegetables, fruits, milk, green tea, coffee and black tea; physical activities such as walking hours per day and sports activities per week; cigarettes smoking and alcohol drinking; body height, body weight at 20 years old and a year before diagnosis, maximum body weight in lifetime, and weight gain in adult age defined as maximum body weight in lifetime minus body weight at 20 years old; own medical history and cancer histories in parents and siblings. All 117 patients filled out the self-administrated questionnaire.

The average age at the time of diagnosis of the 117 patients with PCa was 69.4 years (standard deviation or SD; 6.4 years; Range; 53-82 years). The mean and median interval between the date of the diagnosis and filling out the questionnaire were 1.8 and 1.7 years, respectively (SD; 1.1 years). Their distribution of clinical stages as classified

Table 1. Odds ratios (ORs) and their 95% Confidence Intervals (95%CI) for Prostate Cancer with Regard to Body Stature

Items	Contents	Cases No.	(%)	Controls No.	(%)	OR	95%CI
Body height	<160.0cm	15	(12.8)	31	(11.2)	1.00	
	160.0-164.9cm	37	(31.6)	82	(27.6)	0.90	0.43, 1.89
	165.0-169.9cm	39	(33.3)	97	(35.0)	0.86	0.42, 1.76
	≥170.0	26	(22.2)	67	(24.2)	0.87	0.40, 1.90
	P for trend =0.716						
Body weight	<55.0kg	7	(6.0)	24	(8.7)	1.00	
	55.0-64.9kg	52	(44.4)	125	(45.1)	1.49	0.57, 3.85
	65.0-74.9kg	45	(38.5)	95	(34.3)	1.74	0.65, 4.64
	≥75.0kg	13	(11.1)	33	(11.9)	1.64	0.55, 4.91
	P for trend =0.345						
Body mass index	<21.0	14	(12.0)	39	(14.1)	1.00	
(BMI)	21.0-22.9	29	(24.8)	87	(31.4)	1.05	0.50, 2.21
	23.0-24.9	41	(35.0)	77	(27.8)	1.63	0.77, 3.45
	≥25.0	33	(28.2)	74	(26.7)	1.39	0.66, 2.96
	P for trend=0.071						
Body weight at 20	<50.0kg	3	(2.6)	7	(2.5)	1.00	
years of age	50.0-59.9kg	70	(59.8)	138	(49.8)	1.16	0.28, 4.51
	60.0-69.9kg	38	(32.5)	104	(37.6)	0.84	0.21, 3.41
	≥70.0kg	6	(5.1)	28	(10.1)	0.46	0.09, 2.44
	P for trend =0.063						
BMI at 20 years	<21.0	54	(46.2)	108	(39.0)	1.00	
of age	21.0-22.9	46	(39.3)	104	(37.6)	0.85	0.52, 1.39
	23.0-24.9	11	(9.4)	46	(16.6)	0.47*	0.22, 0.98
	≥25.0	6	(5.1)	19	(6.9)	0.58	0.22, 1.52
	P for trend =0.051						
Maximum body	<60.0kg	6	(5.1)	23	(8.3)	1.00	
weight in lifetime	60.0-69.9kg	55	(47.0)	122	(44.0)	1.70	0.67, 4.32
	70.0-79.9kg	41	(35.0)	86	(31.1)	1.72	0.64, 4.58
	≥80.0kg	15	(12.8)	46	(16.6)	1.36	0.48, 3.85
	P for trend =0.923						
Maximum BMI	<23.0	20	(17.1)	55	(19.9)	1.00	
in lifetime	23.0-24.9	32	(27.4)	72	(26.0)	1.31	0.66, 2.59
	25.0-26.9	35	(29.9)	78	(28.2)	1.16	0.57, 2.33
	≥27.0	30	(25.6)	72	(26.0)	1.22	0.61, 2.41
	P for trend =0.746						
Weight gain in adult	<5kg	18	(15.4)	65	(23.5)	1.00	
age	5.0-9.9kg	24	(20.5)	76	(27.4)	1.22	0.58, 2.55
	10.0-14.9-	43	(36.8)	55	(19.9)	3.55***	1.71, 7.39
	≥15.0kg	32	(27.4)	81	(29.4)	1.73	0.83, 3.59
	P for trend =0.041						

*P<0.05; ***P<0.001; Weight gain in adult age = (Maximum body weight in lifetime) - (Body weight at 20 years of age)

as 28 of stage I, 72 of Stage II, 16 of Stage III and 1 of Stage IV. Also, their distribution of Gleason scores was classified as 45 of Score 6, 43 of Score 7, 17 of Score 8 and 12 of Score 9. Among them, 79 patients had been operated on with a radical prostatectomy, 34 patients had been treated with radiation and 14 patients had been treated with hormone therapy.

Four controls per case, namely, 468 controls, were randomly selected from resident registries as age and address (ward, city or town) matched with each case in March, 2009. Excluding 9 subjects (2 dead, 7 moved out), 318 control subjects (69.5%) gave us informed consent and filled out the same questionnaire as a patient with PCa. Data of 277 control subjects were used for the analysis excluding 41 subjects with previous cancer history. As we did not collect sera from the controls, we could not estimate the risk of the personal characteristic of equol producer or non-producer itself. However, we conducted a stratified analysis according to personal status of equol production among the PCa patients.

The conditional logistic regression model was utilized for analyzing the individually age and address-matched data (Breslow and Day, 1980), and odds ratios (ORs) and their 95% confidence intervals (95%CIs) of potential risk factors for PCa were calculated using the software SAS System (SAS Institute Inc., 1995). The significance level was set at the 5% level. This study was approved by the Institutional Review Board of Sapporo Medical University.

Results

ORs and their 95%CIs for PCa with regard to body statue are shown in Table 1. BMI at 20 years of age of between 23.0 and 24.9 was found to be significantly associated with a reduced risk of PCa (OR=0.47, 95%CI 0.22, 0.98), and a higher BMI at 20 years of age was marginally significantly associated with a decreased risk of PCa (P for trend, P=0.051). Weight gain in adult age between 10.0kg and 14.9kg was noted to be significantly associated with an elevated risk of PCa (OR=3.55, 95%CI 1.71, 7.39), and larger weight gain in adult age was significantly associated with an increased risk of PCa (P for trend, P=0.041).

ORs (their 95%CIs) for PCa with regard to family cancer history are shown in Table 2. History of prostate cancer in fathers or brothers was significantly associated with an increased risk of PCa (OR=9.71, 95%CI 3.59, 26.27), and history of breast cancer in mothers or sisters was also significantly associated with an increased risk of PCa (OR=2.70, 95%CI 1.12, 6.49). Although history of any cancer in fathers was significantly associated with an increased risk of PCa (OR=2.11, 95%CI 1.27, 3.49), this elevated risk became insignificant when history of PCa in fathers was excluded from the analysis (OR=1.53, 95%CI 0.91, 2.57).

Table 2. Odds ratios (ORs) and 95% Confidence Intervals (95%CI) for Prostate Cancer with Regard to Family Cancer History

Items	Content	Cases No.	(%)	Controls No.	(%)	OR	95%CI
Any cancer in fathers							
	No	77	(65.8)	218	(78.7)	1.00	
	Yes	40	(34.2)	59	(21.3)	2.11**	1.27, 3.49
Any cancer in mothers							
	No	88	(75.2)	222	(80.1)	1.00	
	Yes	29	(24.8)	55	(19.9)	1.20	0.72, 2.00
Prostate cancer in fathers or brothers							
	No	97	(82.9)	272	(98.2)	1.00	
	Yes	20	(17.1)	5	(1.8)	9.71***	3.59, 26.3
Breast cancer in mothers or sisters							
	No	106	(90.6)	266	(96.0)	1.00	
	Yes	11	(9.4)	11	(4.0)	2.70*	1.12, 6.49
Uterine cancer in mothers or sisters							
	No	110	(94.0)	266	(96.0)	1.00	
	Yes	7	(6.0)	11	(4.0)	1.24	0.47, 3.28
Colorectal cancer in parents or siblings							
	No	100	(85.5)	254	(91.7)	1.00	
	Yes	17	(14.5)	23	(8.3)	1.88	0.97, 3.64
Pancreatic cancer in parents or siblings							
	No	111	(94.9)	266	(96.0)	1.00	
	Yes	6	(5.1)	11	(4.0)	1.31	0.46, 3.71
Bile duct cancer in parents or siblings							
	No	114	(97.4)	276	(99.6)	1.00	
	Yes	3	(2.6)	1	(0.4)	7.29	0.74, 71.7

*P<0.05; **P<0.01; ***P<0.001

Frequency of consumption of soybean products, such as tofu and natto, as well as the other surveyed foods or beverages were not associated with risk of PCa. None of the other variables, such as physical activities, cigarette smoking, alcohol drinking or various foods consumption were associated with risk of PCa, either.

The Spearman's correlation coefficients (r) in clinical status and risk factors among the 117 PCa patients are shown in Table 3. Age was significantly negatively correlated with history of PCa in fathers or brothers (r=-0.196, P<0.05). The Gleason score was significantly positively correlated with clinical stage (r=0.229, P<0.05). Weight gain in adult age was significantly negatively

Table 3. Spearman's Correlation Coefficients for Clinical Status and Risk Factors among 117 Prostate Cancer Patients

	1. AG	2. ST	3. GS	4. BMI20	5. WG	6. PCaFB
1. Age (AG)	1.000					
2. Stage (ST)	-0.032	1.000				
3. Gleason score (GS)	-0.071	0.229*	1.000			
4. BMI at 20 years (BMI20)	0.166	0.075	0.161	1.000		
5. Weight gain in adult age (kg) (WG)	-0.144	0.048	0.069	-0.275*	1.000	
6. Prostate cancer in fathers or brothers[1]	-0.196*	-0.119	-0.085	-0.063	0.054	1.000
7. Breast cancer in mothers or sisters[2]	-0.019	0.049	0.001	0.052	-0.272**	0.001

[1](Number) (PCaFB); [2](Number) (BCaMS); *P<0.05; **P<0.01

correlated with BMI at 20 years of age (r=-0.275, P<0.05) as well as history of breast cancer in mothers or sisters (r=-0.272, P<0.01).

Discussion

We found that higher BMI at 20 years old was associated with a marginally significantly reduced risk of PCa, and larger weight gain in adult age was significantly associated with an increased risk for PCa. Similarly, Write at al. (2007) also showed that higher baseline BMI was associated with a significantly reduced incidence of PCa, and larger weight gain from 18 years old was significantly positively associated with a risk of PCa mortality in a large cohort study.

As total energy intake was shown to be positively associated with risk of PCa (Andersson et al., 1996; Grönberg et al., 1996a; Hsieh et al., 2003; Kristal et al., 2003) increased risk of PCa by larger weight gain in adult age might be achieved through high total energy intake and low physical activity. However, we did not get information of total energy intake. Association of physical activities with reduced PCa risk was not observed in our brief questions either.

Some studies (Bradbury et al., 2005; Porter and Stanford, 2005) have suggested a significantly negative association of BMI with PCa risk. On the contrary, other studies (Grönberg et al., 1996; Rodriguez et al., 2001; Dal Maso et al., 2004; Engeland et al., 2003) have indicated a significantly positive association of BMI with risk of PCa. Difference of stage, grade or aggressiveness may provide an explanation of the conflict in these results of the relationship between obesity and PCa risk (Gong et al. 2006), (MacInnis et al., 2003; Littman et al., 2007; Rodriguez et al., 2007). Most of the reports have shown that BMI is inversely associated with the risk of nonmetastatic and low-grade PCa, but BMI is positively associated with the risk of metastatic or high-grade PCa. However, clinical stage or Gleason's score were not correlated with BMI at 20 years of age or weight gain in adult age in our study, as shown in Table 3.

The complex relationship of weight gain in adult age or BMI at 20 years of age with PCa risk has been suggested to be caused by conflict in hormonal role of development of PCa (Rodriguez et al., 2001; 2007; Dal Maso et al., 2004; Gong et al., 2006; Wright et al. 2007). Larger weight gain in adult age may be associated with higher insulin, leptin, free IGF-I and lower sex hormone-binding globulin concentrations, which could possibly increase the risk of PCa. Conversely, higher BMI at 20 years of age may be associated with lower circulating testosterone concentrations and higher estrogen concentrations, which could decrease the risk of PCa.

History of PCa in first-degree relatives is an established risk factor for PCa (Ghadirian et al., 1991; Carter et al., 1992; Grönberg et al., 1996b; Lesko et al., 1996; Ghadirian et al., 1997; Cerhan et al., 1999; Eldon et al., 2003; Karakiewicz et al., 2003; Negri et al., 2005). The reported range of risk ratios in family history of PCa varied from 1.7 to 8.7. The reason of a higher odds ratio (OR=9.71) in our study than in other studies is not able to be clearly explained, but it may be a part of the reason that nature of the control group was not hospital-based, but population-based. However, some extent of recall bias in the study subjects cannot be ruled out.

History of PCa in fathers or brothers was inversely correlated with age at onset in our study, as it has been similarly reported that risk of family history of PCa is prominent in younger age groups (Eldon et al., 2003; Carter et al., 1992; Grönberg et al., 1996b; Lesko et al. 1996). Although Spangler et al. (2005) suggested that family history of PCa may be associated with predictors of deteriorated clinical outcome, family histories of PCa were not correlated with clinical stage or Gleason's score in our study. Although Giovannucci et al. (2003) a found significantly inverse correlation between BMI and a family history of PCa, either of BMI at weight or gain in adult age was not correlated with family history of PCa in our study, as shown in Table 3.

History of breast cancer in first-degree relatives has also been reported as a significant risk factor for PCa (Cerhan et al., 1999; Grönberg et al., 2000; The Breast Cancer Linkage Consortium, 1999), although the other studies have shown no association between family history of breast cancer and PCa risk (Eldon et al., 2003; Karakiewicz et al., 2003; Negri et al. 2005). In a report from the Breast Cancer Linkage Consortium (1999), the risk ratio of PCa in BRCA2 carriers was 4.65 (95%CI 3.48, 6.22). A significantly inverse correlation between weight gain in adult age and history of breast cancer in mothers or sisters was observed in our study, although similar result have not been reported in previous studies.

To our knowledge, this is the first case-control study of PCa using population-based controls in Japan. However, there were some limitations in our study. First, the sample size of the study was not large enough, especially, to assess the interaction between the host and environmental factors. Although we previously reported the preventive effects of soybean products or isoflavones for PCa (Nagata et al. 2007), we could not detect any risk or preventive dietary factors in this study. The reason for such null findings might be from the small sample size in addition to the methodological limitation of the survey that we did not collect information on the amount of food consumptions. Second, response from the study subjects was not perfect. However, a relatively high response rate was obtained not only from the cases (82.3%), but also from the controls (69.5%). Third, we used self-reported weight, height and family history of cancer, all of which are subject to error. However, it has been shown that self-reported weight and height were highly valid compared with measured values (Stevens et al. 1990), and self reported cancer in a first-degree relative was relatively accurate (Whittemore et al., 1995).

In conclusion, the recent increase in the incidence rate of PCa may have possibly been brought about by an increased proportion of Japanese men with larger weight gain in adult age.

Acknowledgements

This study was supported by Grant-in Aid for Scientific

Research (B) No. 19390176 from Japan Society for the Promotion of Science (JSPS). No conflict of interest is declared.

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