RESEARCH ARTICLE

Cigarette Smoking and Prostate Cancer Risk: Negative Results of the Seoul Male Cancer Cohort Study

Jong-Myon Bae[1]*, Zhong-Min Li[2], Myung-Hee Shin[3], Dong-Hyun Kim[4], Moo-Song Lee[5], Yoon-Ok Ahn[6]

Abstract

We evaluated cigarette smoking as a risk factor for prostate cancer in a prospective, population-based cohort study. The subjects were 14,450 males among the participants in the Seoul Male Cancer Cohort Study who had at least 1-year follow-up. They were followed up between 1993 and 2008. During the 16-year follow-up period, 87 cases of prostate cancer occurred over the 207,326 person-years of the study. The age-adjusted relative risks of past and current smokers at entry were 0.60 (95%CI: 0.34-1.06) and 0.70 (95%CI: 0.43-1.13), respectively, suggesting that cigarette smoking may not be a risk factor for prostate cancer. The relationship between prostate cancer and other modifiable factors, such as Westernized diet, should be studied with the goal of establishing prevention programs for prostate cancer.

Keywords: Prostate neoplasms - cancer incidence - cigarette smoking - cohort study

Asian Pac J Cancer Prev, **14 (8)**, 4667-4669

Introduction

Prostate cancer is the most frequently diagnosed cancer among men in developed countries and has the second highest incidence worldwide (Jemal et al., 2011). Migrant studies demonstrating an increase in the incidence of prostate cancer among men who move from low- to high-incidence countries (Cook et al., 1999) suggest that environmental factors may play a role in the development of prostate cancer.

Smoking is a modifiable environmental factor that may increase the risk of prostate cancer because cigarettes contain several known carcinogens and have been reported to increase circulating levels of androgens in men (Pour, 1919; Dai et al., 1988). Huncharek et al. (2010) argued an association between smoking and the incidence of prostate cancer in a meta-analysis of 24 prospective cohort studies. However, one of their results showed no increase in the risk of cancer in current smokers.

Previous observational studies of the link between smoking and prostate cancer in humans have yielded inconsistent results, and the incidence of prostate cancer varies widely according to race and ethnicity (Huncharek et al., 2010; Mordukhovich et al., 2011); thus, the present study used a population-based, prospective cohort design to evaluate the relationship between smoking habits and the risk of prostate cancer in Korean men.

Materials and Methods

Study cohort

The source population was the participants of the Seoul Male Cancer Cohort (SMCC) study, which has been reported elsewhere (Bae et al., 2002; 2007; 2013). The cohort was constructed in 1992 and 1993 for investigating the association between exposure to modifiable lifestyle factors and the risk of major cancers in Korean men. The age distribution of this cohort is similar to that of the Korean population. After excluding subjects with less than 1-year follow-up, 14,450 men were included in the present study.

A 15-page confidential questionnaire including questions on smoking habits was used to collect information about smoking status (never, past, current), duration of smoking (years), and daily amount of smoking (cigarettes/day). The reproducibility and validity of the questionnaire was evaluated in a subset of participants (Kim et al., 1996).

Follow-up was conducted over the 16-year period between January 1, 1993, and December 31, 2008. The incidence of all cases of cancer, including prostate cancer, occurring during the 16-year follow-up period were identified using the Seoul Regional Cancer Registry (SRCR) database, a population-based cancer registry (Parkin et al., 2002); the Korea Central Cancer Registry

[1]*Department of Preventive Medicine, Jeju National University, School of Medicine, Jeju,* [3]*Department of Social and Preventive Medicine, Sungkyunkwan University School of Medicine, Suwon,* [4]*Department of Social Mediicine, Hallym University College of Medicine, Chuncheoun,* [5]*Department of Preventive Medicine, Ulsan University College of Medicine,* [6]*Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea,* [2]*Department of Epidemiology and Statistics, Jilin University School of Public Health Science, Changchun, China *For correspondence: jmbae@jejunu.ac.kr*

(KCCR), a nationwide, hospital-based, cancer registry (KCCR, 2013); and death certificates from Statistics Korea, 2013 (http://www.kostat.go.kr/portal/english/resources/2/4/1/index.static).

Categorization of variables

Subjects were categorized at entry according to age (40-44, 45-49, 50-54, and 55-59 years), duration of smoking (0, 1-10, 11-20, 21-30, or 31+ years), daily amount of smoking (0, 1-10, 11-20, 21-30 or 31+ cigarettes/day), and total cigarette index (TCI) obtained from smoking duration times daily amount of smoking (0, 1-10, 11-15, 16-20, 21-34 or 35+ packs/year).

Statistical methods

Accumulated person-years were calculated by determining the number of days from the initiation of follow-up, January 1, 1993, until the date of cancer diagnosis, death from other causes, or the end of the follow-up period, December 31, 2008, after which the number of days was converted into years. The age-adjusted relative risk (aRR) was calculated using the Cox proportional hazards regression. Confidence intervals were obtained using the Wald method, and all reported p values are two-sided. The chi-squared test for trends was used to evaluate linear trends. Analyses were conducted using Stata software ver. 12 (StataCorp, 2013) (http://www.stata.com/).

Ethics statement

The study protocol was approved by the Institutional Review Board of the Seoul National University College of Medicine (IRB No. C-1193-146-357).

Results

Table 1 shows the distribution of participants by age and smoking status at entry into the study and the accumulated person-years of follow-up. During the total 207,326 person-years of follow-up, 87 newly diagnosed cases of prostate cancer were identified in the 14,450 study participants. Because the risk of prostate cancer was strongly age-dependent, the aRR were calculated using Cox's proportional hazard model.

Table 2 shows the estimated aRRs and 95% CIs according to smoking history at entry. The risk of prostate cancer was slightly lower for past (aRR, 0.60) and current smokers (aRR, 0.70) compared to never-smokers, although the difference was not statistically significant. We found no significant effect of duration of smoking, amount of daily smoking, or total cigarette index on the aRR of prostate cancer, with the exception of 21-30 years of smoking duration. However, no significant trend with regard to the smoking duration was observed (p for

Table 1. The Seoul Male Cancer Cohorts Follow-up Study*

Age at entry (years)	No. of subjects (col%)	Person-years	Cases (col%)	No. (row%) by smoking status at entry**		
				Never	Ex	Current
40-44	4,958 (34.3)	72,785	8 (9.2)	1,026 (21.0)	1,247 (25.5)	2,616 (53.5)
45-49	4,214 (29.2)	60,810	24 (27.6)	915 (22.2)	1,082 (26.2)	2,130 (51.6)
50-54	3,578 (24.7)	50,484	40 (46.0)	852 (24.5)	970 (27.9)	1,652 (47.6)
55-59	1,700 (11.8)	23,247	15 (17.2)	405 (24.5)	506 (30.6)	745 (44.9)
All ages	14,450 (100.0)	207,326	87 (100.0)	3,198 (22.6)	3,805 (26.9)	7,143 (50.5)

*Number of subjects recruited in 1993 and accumulated person-years during follow-up for prostate cancer incidence through 2008, according to age at entry and smoking status. **Excluding missing data (N=304, 2.01%)

Table 2. Age-Adjusted Relative Risk (aRR) and 95% Confidence Intervals (CI) for Prostate Cancer Incidence through 2008 among Seoul Male Cancer Cohorts According to Smoking History at Entry into the Cohort in 1993*

Variables		No. of subjects (col%)	Person-years	No. of cases	aRR	95% CI	p value (χ^2 trend)
Smoking status	Never	3,198 (22.6)	46,391	29	ref		0.12
	Past	3,805 (26.9)	54,771	19	0.6	(0.34, 1.06)	
	Current	7,143 (50.5)	101,776	38	0.7	(0.43, 1.13)	
Duration of smoking	0	3,796 (26.3)	54,851	34	ref		0.06
(years)	1-10	767 (5.3)	11,122	1	0.16	(0.02, 1.20)	
	11-20	1,703 (11.8)	24,699	10	0.82	(0.40, 1.66)	
	21-30	5,193 (35.9)	74,876	20	0.56	(0.32, 0.99)	
	31+	3,001 (20.7)	41,781	22	0.63	(0.36, 1.08)	
Amount of daily smoking	0	3,668 (25.4)	53,152	30	ref		0.3
(cigarettes/day)	1-10	1,235 (8.6)	17,941	6	0.65	(0.27, 1.57)	
	11-20	3,826 (18.4)	54,847	16	0.55	(0.30, 1.01)	
	21-30	4,446 (30.8)	63,331	30	0.89	(0.54, 1.48)	
	31+	1,275 (8.8)	18,055	5	0.53	(0.21, 1.37)	
Total cigarette Index	0	3,393 (24.7)	49,235	29	ref		0.26
(pack-year)	1-10	2,173 (15.9)	31,385	8	0.53	(0.24, 1.14)	
	11-15	1,390 (10.1)	20,033	4	0.41	(0.14, 1.14)	
	16-20	1,572 (11.5)	22,575	12	1.08	(0.56, 2.09)	
	21-34	3,683 (26.9)	52,598	21	0.75	(0.43, 1.29)	
	35+	1,498 (10.9)	20,859	8	0.55	(0.25, 1.19)	

*Excluding missing data

Table 3. Smoking and Prostate Cancer*

Study (Reference)**	Follow-up years	RR	95%CI
Allen et al. (24)	33	0.8	(0.60, 1.07)
Engeland et al. (28)	27	1.1	(0.9, 1.3)
Severson et al. (43)	21	0.87	(0.61, 1.23)
Adami et al. (22)	20	1.11	(1.01, 1.23)
Rohrmann et al. (42)	19	1	(0.63, 1.59)
Giovannucci et al. (29)	16	0.98	(0.89, 1.07)

*Relative risk (RR) in current smokers and 95% confidence interval (CI) after restricting cohort studies with reporting RRs with incidences after a follow up of at least 16 years according to Table 1 in Huncharek et al. (5). **Reference number in Huncharek et al. (2010)

trend=0.06).

Discussion

Our results suggest that smoking may not be a relevant risk factor for prostate cancer in Korean men. This finding is supported by a previous study (Levi and La Vecchia, 2001) that reported that minor long-term changes in prostate cancer mortality rates follow a habitual change in cigarette smoking over time in various countries, whereas mortality rates from lung and other tobacco-related neoplasms change substantially. Furthermore, Leitzmann and Rohrmann (2012) argued that the decreased risk of prostate cancer among smokers may be explained by lower PSA levels in smokers than in non-smokers (Singer et al., 2008), and a lower likelihood that smokers will undergo regular prostate cancer screening examinations compared to non-smokers.

We explored the disparity between the results of our 16-year follow-up study and those of the meta-analysis conducted by Huncharek et al. (2010) by selecting six cohort studies that reported RRs with cancer incidences after at least a 16-year follow up in Table 1 of that previous study. As shown Table 3, the results of five of the six cohorts were consistent with our findings. Thus, results of long-term follow-up studies seem to be more valid given that the incidence of prostate cancer is age related.

Despite the prospective nature of our study, two limitations should be considered when interpreting the results. The first is related to the effect of changes in participant smoking habits during the follow-up period. For example, quitting smoking may have resulted in an underestimation of the RR (Bae et al., 2013). The second is that we did not assess patients according to disease severity. Although current smoking has been reported to be associated with the risk of fatal prostate cancer (Zu and Giovannucci, 2009), we were unable to assess disease severity because a Gleason score was available for only 25% of the prostate cancer patients (Mondul et al., 2011).

In conclusion, cigarette smoking was not found to be a risk factor for prostate cancer in Korean men, indicating that etiological factors other than smoking underlie the incidence of prostate cancer. In Korea, the annual change in incidence rates of prostate and breast cancer were 12.6% and 6.0% between 1999 and 2010, respectively (KCCR, 2013). This suggests that the increasing trend in the incidence of prostate and breast cancer in Korea may be the result of a Westernized diet (Coffey, 2001). Thus, a study of the relationship between dietary factors, particularly fat intake, and prostate cancer is warranted.

Acknowledgements

This study was supported by the 2013 scientific promotion program funded by Jeju National University (2013-0144).

References

Bae JM, Ahn YO (2002). A nested case-control study on the high-normal blood pressure as a risk factor of hypertension in Korean middle-aged men. *J Korea Med Sci*, **17**, 328-36.

Bae JM, Lee MS, Shin MH, et al (2007). Cigarette smoking and risk of lung cancer in Korean men: the Seoul male cancer cohort study. *J Korean Med Sci*, **22**, 508-12.

Bae JM, Li ZM, Shin MH, et al (2013). Lung cancer incidence by smoking status in Korean men: 16-years of observations in the Seoul male cancer cohort study. *J Korea Med Sci*, **28**, 636-7.

Coffey DS (2001). Similarities of prostate and breast cancer: evolution, diet, and estrogens. *Urology*, **57**, 31-8.

Cook LS, Goldoft M, Schwartz SM, Wiess NS (1999). Incidence of adenocarcinoma of the prostate in Asian immigrants to the United States and their descendants. *J Urol*, **161**, 152-5.

Dai WS, Gutai JP, Kuller LH, Cauley JA (1988). Cigarette smoking and serum sex hormones in men. *Am J Epidemiolm*, **128**, 796-805.

Huncharek M, Haddock KS, Reid R, Kupelnick B (2010). Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. *Am J Public Health*, **100**, 693-701.

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.

Korea Central Cancer Registry in National Cancer Center (2013). Cancer Statistics. available at http://ncc.re.kr/english/infor/kccr.jsp.

Kim MK, Lee SS, Ahn YO (1996). Reproducibility and validity of a self-administered semiquantitative food frequency questionnaire among middle-aged men in Seoul. *Korean J Community Nutr*, **1**, 376-94.

Leitzmann MF, Rohrmann S (2012). Risk factors for the onset of prostatic cancer: age, location, and behavioral correlates. *Clin Epidemiol*, **4**, 1-11.

Levi F, La Vecchia C (2001). Tobacco smoking and prostate cancer: time for an appraisal. *Ann Oncol*, **12**, 733-8.

Mondul AM, Weinstein SJ, Virtamo J, Albanes D (2011). Serum total and HDL cholesterol and risk of prostate cancer. *Cancer Causes Control*, **22**, 1545-52.

Mordukhovich I, Reiter PL, Backes DM, et al (2011). A review of African American-white differences in risk factors for cancer: prostate cancer. *Cancer Causes Control*, **22**, 341-57.

Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (2002). Cancer Incidence in Five Continents, vol. VIII. IARC Sci Publisher, Lyon, pp 276-7.

Pour PM (1919). A new prostatic cancer model: systematic induction of prostate cancer in rats by a nitrosamine. *Cancer Lett*, **13**, 303-8.

Singer EA, Palapattu GS, van Wijngaarden E (2008). Prostate-specific antigen levels in relation to consumption of nonsteroidal anti-inflammatory drugs and acetaminophen: results from the 2001-2002 national health and nutrition examination survey. *Cancer*, **113**, 2053-7.

Zu K, Giovannucci E (2009). Smoking and aggressive prostate cancer: a review of the epidemiologic evidence. *Cancer Causes Control*, **20**, 1799-810.