Published in final edited form as:
Urology. 2007 April ; 69(4): 721–725. doi:10.1016/j.urology.2006.12.020.

Smoking and risk of fatal prostate cancer in a prospective US study

Sabine Rohrmann[a,b], **Jeanine M Genkinger**[c], **Alyce Burke**[a,d], **Kathy J Helzlsouer**[a,d,e,f], **George W Comstock**[a,d], **Anthony J Alberg**[a,d,e], and **Elizabeth A Platz**[a,e,g]

[a] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[b] Division of Clinical Epidemiology, German Cancer Research Center, Heidelberg, Germany

[c] Department of Nutrition, Harvard School of Public Health, Boston, MA, USA

[d] George W. Comstock Center for Public Health Research and Prevention, Hagerstown, MD, USA

[e] Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

[f] Mercy Medical Center, Baltimore, MD USA

[g] James Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, MD, USA

Abstract

Objective—To examine the association of cigarette smoking with subsequent fatal prostate cancer.

Methods—Two private censuses were conducted in Washington County, Maryland, in which 26,810 adult men in 1963 and 28,292 in 1975 provided smoking information. Prostate cancer deaths through 2002 (1963 cohort: 240 deaths; 1975 cohort: 184) were ascertained by review of death certificates. Poisson regression was used to estimate the rate ratio (RR) of prostate cancer death adjusted for age.

Results—Overall, cigarette smokers in the 1963 census cohort were not more likely to die from prostate cancer than never smokers of cigarettes, pipes, and cigars when considering total follow-up. However, current smokers of 20+ cigarettes per day (RR = 2.38; 95% CI 0.94–5.99) and former smokers (RR = 2.75; 95% CI 1.13–6.74) had a higher risk of death from prostate cancer during the first 10 years of follow-up. Weaker positive associations of prostate cancer death with current and former cigarette smoking were seen during the first 10 years of follow-up in the 1975 census cohort. Current cigarette smoking at baseline was not associated with prostate cancer incidence.

Conclusion—The lack of an association of cigarette smoking with prostate cancer incidence, but the tendency of a higher prostate cancer mortality in former and current cigarette smokers earlier in follow-up is consistent with other studies in which smoking was assessed once at baseline.

Correspondence: Elizabeth A. Platz, Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, 615 N. Wolfe St., Rm. E 6138, Baltimore, MD 21205, phone +1 410 614 9674, fax +1 410 614 2632, eplatz@jhsph.edu.

Introduction

The prevalence of cigarette smoking has decreased in the US, but smoking is still common in the US, with 23.1% of adult men smoking in 2004.[1] Cigarette smoking does not appear to be a risk factor for prostate cancer incidence overall,[2] although some studies have noted positive association with incidence.[3] However, the evidence for an association between cigarette smoking and prostate cancer mortality is more intriguing. Several,[4–7] but not all,[8–10] cohort studies observed a statistically significant positive association between cigarette smoking and prostate cancer mortality. Thus, we evaluated the association of cigarette smoking habits with subsequent prostate cancer incidence and mortality using the data from two private censuses conducted in 1963 and 1975 in Washington County, Maryland. These two censuses offered the opportunity to examine this association in a group of men with decades of follow-up.

Methods

Participants

In 1963, 91,909 persons representing 98% of Washington County's households participated in the census. Of these 27,764 were adult men (18+ years old). In 1975 90,225 Washington County inhabitants (about 90% of the county's households in 1975) participated in the census, and of these 29,493 were men 18 years of age or older.

Exposure assessment

In the 1963 census, participants 18 years and older were asked whether they currently or formerly smoked cigarettes, if they had ever smoked cigars or pipes, and the age when smoking started. The number of cigarettes smoked per day was assessed in three categories (<10, 10–19, 20+ cigarettes per day). Of the 27,764 adult male respondents, 26,810 provided information on smoking habits (96.6%). In the 1975 census adults were asked if they currently or formerly smoked cigarettes, if they currently smoked cigars or pipes, and the number of cigarettes they smoked per day. Of the 29,376 adult male respondents 28,292 provided smoking information (96.3%).

Exposure to passive smoking in the household was assessed. Men were classified as not exposed to passive smoke if no household member smoked. In the 1963 census cohort, only 1555 men were exposed to passive smoking and were not active smokers. Among those men, no prostate cancer cases occurred. Thus, for the purpose of our analysis, men were classified as never smokers irrespective of their passive smoking exposure. The same was done for the 1975 census group. In both censuses, information was collected on age, years of education, and marital status.

Outcome Assessment and Statistical Analysis

Deaths from prostate cancer were ascertained from information reported to the Washington County Health Department using the underlying cause of death as coded by the Maryland Department of Health and Mental Hygiene. Men were censored at date of death, at the date of cancer diagnosis, or at the end of the study period in 2000, whichever came first.

Incident prostate cancer cases were ascertained by linkage to the Washington County Cancer Registry, which was established in 1948. Because the participants in the two censuses were not under active follow-up, a method was devised to account for the likelihood of moving out of the county and, thus, being no longer under passive surveillance by the Washington County Cancer Registry for cancer diagnosis. A follow-up survey to assess the likelihood of still being a Washington County resident was conducted in July 1971 for the 1963 census cohort and in July 1985 for the 1975 census cohort. Each comprised a 5% random sample of the households

in the censuses. The probability of still living in Washington County was estimated for those in the 5% random sample based on their age, marital status, gender, education, and smoking status from a linear regression model. These coefficients for the predictive characteristics were then applied to each census participant to estimate the likelihood that a given individual was still living in Washington County. We limited the observation time to a period for which it was reasonable to assume that this calculated likelihood of still living in Washington County was valid: The time between the 1963 census and the 1971 follow-up survey and the time between the 1975 census and the 1985 follow-up survey, respectively, were doubled to create the maximum observation time. Thus, the maximum observation time for the 1963 census cohort was taken to be the 15 years until 1978 and for the 1975 census cohort, the 19 years until 1994. We multiplied the maximal observation time by the probability factor to correct for the probability of still living in Washington County.

Analyses of prostate cancer death and prostate cancer incidence were done according to the smoking status (never, former, current cigarette smoker, pipe/cigar smoker only) at the time of the censuses in 1963 and 1975, respectively. Current smokers further were classified according to the number of cigarettes smoked per day. We calculated rate ratios (RR) and 95% confidence intervals (CI) of prostate cancer mortality (1963 to 2000 or 1975 to 2000) or incidence (1963 to 1978 or 1975 to 1994) using Poisson regression. Because age was a strong negative confounder in these data, we controlled finely for age by entering it into the model as a continuous term. Further adjustment for education and marital status did not change the RRs appreciably. Therefore, multivariable RRs are not shown. All analyses were conducted using SAS version 8.01 (SAS Institute, Cary, North Carolina).

Results

In the 1963 census, more than 50% of adult men were current smokers; only 14.5% reported neither active nor passive smoking exposure (Table 1). In contrast, the proportion of never active and never passive smoking was higher on the second census in 1975, while the percentage of current smokers was lower than in the 1963 census. During the truncated and weighted follow-up time of 15 years of the 1963 census cohort, 147 incident prostate cancer cases were ascertained. During the truncated and weighted follow-up time of 19 years of the 1975 census cohort, 351 incident prostate cancer cases were ascertained. For prostate cancer death, we did not truncate or weight the follow-up period; of the men who participated in the 1963 census, 240 died of prostate cancer between 1963 and 2000, and of the 1975 census participants 185 men died of this disease between 1975 and 2000.

Current cigarette smoking was not statistically significantly associated with prostate cancer incidence in either census cohort (Table 2). However, current cigarette smokers who smoked at least 20 cigarettes per day had a non-significantly elevated risk of prostate cancer in both censuses. Also, we observed a moderately, but not statistically significantly increased risk of prostate cancer in former cigarette smokers and in ever cigar/pipe smokers in the 1963 census. No association with former cigarette smoking or with current cigar/pipe smoking was seen in the 1975 census cohort. No statistically significant associations between cigarette or pipe/cigar smokers and incident prostate cancer were observed when considering only the first 10 years of follow-up (Table 2).

Considering the total observation time until 2000 (37 years for the 1963 census cohort and 25 years for the 1975 census cohort), we did not observe an association between cigarette smoking or cigar/pipe smoking and the risk of dying from prostate cancer in either of the two census cohorts (Table 3). However, when including only the first ten years of follow-up of the 1963 census cohort, former smokers were more likely to have died from prostate cancer than never smokers (Table 3). We observed a non-significantly increased risk of prostate cancer death for

current smokers; this association was strongest in men who smoked 20+ cigarettes per day. Positive associations for current and former cigarette smoking were also observed in the 1975 census cohort, although of lesser magnitude than in the 1963 census.

Discussion

In this prospective US study, we did not observe statistically significant associations between cigarette or cigar/pipe smoking and prostate cancer mortality or incidence. However, current and former cigarette smokers tended to have a higher risk of dying from prostate cancer during the first ten years of follow-up than never smokers.

Only a few studies were able to investigate prostate cancer mortality and incidence over several decades of follow-up.[5,7,9,11,12] Our finding of no association between cigarette smoking and prostate cancer incidence is compatible with the majority of other studies of this association, although some studies have noted positive association with incidence.[3]

Prostate cancer mortality was positively associated with cigarette smoking in several large cohort studies.[4–7,11] We observed an elevated risk of prostate cancer mortality when we considered the first ten years of follow-up, but not when considering total follow-up. This has been reported previously.[4] It might be that the extent of misclassification of smoking status is less earlier in follow-up when using the baseline smoking status (i.e., census report) than later in follow-up, when men may have subsequently quit smoking. One year after the 1963 census the first US Surgeon General's Report on the health consequences of smoking was released.[13] According to the 1989 US Surgeon General's Report[14] 40% of men who were smokers in the mid 1960s quit smoking within the next 20 years. Of 7,868 men who were current smokers in the 1963 census and who participated in the 1975 census, 30.1% had quit smoking. Assuming that misclassification of smoking status would be non-differential with respect to future risk of death from prostate cancer, a possible association between smoking and prostate cancer mortality would be underestimated. In a study by Hsing et al.,[11] a statistically significant higher risk of fatal prostate cancer was observed after 26 years of follow-up. However, with duration of the follow-up the relative risk of dying from prostate cancer in smokers compared to never smokers was increasingly attenuated.

Male smokers have higher serum estrogen concentration than non-smokers[15] and smoking is associated with an increased estrogen 2-hydroxylation in the liver causing the formation of 2-hydroxyestrogens. The increase in these estrogen metabolites with low estrogen activity[16] may induce a more aggressive phenotype in the subset of prostate tumors that are hormone-sensitive and, thus, increase the risk of death from prostate cancer.[17] Smoking might cause mutations in genes like p53, which may enhance the aggressive behavior of the tumor.[4] Cigarette smoke carcinogens like heterocyclic aromatic amines and polycyclic aromatic hydrocarbons are metabolized and inactivated by glutathione *S*-transferase pi,[18] which is absent in most prostate cancers.[19] This loss could increase the likelihood of damage through continued exposure of the nascent prostate tumor to cigarette smoke carcinogens, resulting in the promotion of more rapidly progressing prostate cancer.[20] Alternatively, we cannot exclude that the higher risk of death due to prostate cancer is caused by a combination of higher mortality in smokers and a mis-attribution of death due to prostate cancer close in time to the time of prostate cancer diagnosis. However, most of the follow-up time in this study occurred in the era prior to the routine screening for elevated PSA when the cases were more likely to have been detected at a clinically advanced stage, and, thus, more likely to have resulted in death.

Former smokers who had recently quit smoking had a higher risk of dying from prostate cancer in the Health Professionals Follow-up Study.[4] We also observed an increased risk of prostate cancer death among former smokers, but we did not have information about when these men

stopped smoking and could not determine if the risk would be higher in men who had quit recently compared to men who had quit a longer time prior to the censuses.

Only older age, African-American race, and a family history of prostate cancer have consistently been identified as risk factors for prostate cancer. We finely controlled for age in this analysis and the two cohorts were predominantly Caucasian. Information on family history of prostate cancer was not available, but the lack of adjustment for this is unlikely to have confounded our results because family history of prostate cancer is unlikely to be strongly correlated with smoking.

Cancer diagnosis was ascertained from the Washington County cancer registry. To be captured by this registry, individuals must have resided in Washington County. In the analysis of prostate cancer incidence, we accounted for different probabilities of moving out of Washington County. By limiting our analysis to a short period of time and by including moving probabilities we tried to minimize the consequences of loss to follow-up that was differential by smoking status. Smokers were more likely to have moved out of Washington County, but any remaining differential loss to follow-up that we could not account for would have been more likely to have produced an underestimate of the smoking prostate cancer association than an overestimation of the calculated risks. We did not apply the probability weights or restrict the follow-up for the prostate cancer deaths analysis since deaths were ascertained through a mechanism that was not restricted to those men who were very likely still living in Washington County. Thus, the prostate cancer deaths analysis had greater power than the prostate cancer incidence analysis to detect an association for smoking.

In conclusion, no association of cigarette smoking with prostate cancer incidence or mortality overall was observed with long-term follow-up of respondents to two private censuses in Washington County, MD. However, our finding of a higher risk of fatal prostate cancer early in follow-up warrants further investigations into the effects of recent smoking on prostate cancer. Future studies evaluating the long-term effects of smoking on prostate cancer require multiple assessments of smoking status over time to minimize the possibility of misclassification of smokers and non-smokers.

Acknowledgments

This study is supported by the Cigarette Restitution Fund at Johns Hopkins University (to Dr. Alberg). Dr Rohrmann is supported by the Fund for Research and Progress in Urology, Johns Hopkins Medical Institutions. Dr. Comstock is partly supported by the Research Career Award (HL21760).

These data were supplied in part by the Maryland Cancer Registry, the Department of Mental Hygiene, Baltimore, Maryland. The Department of Health and Mental Hygiene specifically disclaims responsibility for any analyses, interpretations or conclusions.

References

1. National Center for Chronic Disease Prevention & Health Promotion. Behavioral Risk Factor Surveillance System: Current smoking nationwide. 2002 [(last access 04/28/2006)]. http://apps.nccd.cdc.gov/brfss/sex.asp?cat=TU&yr=2002&qkey=4396&state=UB
2. U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.
3. Hickey K, Do KA, Green A. Smoking and prostate cancer. Epidemiol Rev 2001;23:115–25. [PubMed: 11588835]

4. Giovannucci E, Rimm EB, Ascherio A, Colditz GA, Spiegelman D, Stampfer MJ, Willett WC. Smoking and risk of total and fatal prostate cancer in United States health professionals. Cancer Epidemiol Biomarkers Prev 1999;8:277–82. [PubMed: 10207628]
5. Coughlin SS, Neaton JD, Sengupta A. Cigarette smoking as a predictor of death from prostate cancer in 348,874 men screened for the Multiple Risk Factor Intervention Trial. Am J Epidemiol 1996;143:1002–6. [PubMed: 8629606]
6. Rodriguez C, Tatham LM, Thun MJ, Calle EE, Heath CW Jr. Smoking and fatal prostate cancer in a large cohort of adult men. Am J Epidemiol 1997;145:466–75. [PubMed: 9048521]
7. Hsing AW, McLaughlin JK, Schuman LM, Bjelke E, Gridley G, Wacholder S, Chien HT, Blot WJ. Diet, tobacco use, and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study. Cancer Res 1990;50:6836–40. [PubMed: 2208150]
8. Lotufo PA, Lee IM, Ajani UA, Hennekens CH, Manson JE. Cigarette smoking and risk of prostate cancer in the physicians' health study (United States). Int J Cancer 2000;87:141–4. [PubMed: 10861465]
9. Adami HO, Bergstrom R, Engholm G, Nyren O, Wolk A, Ekbom A, Englund A, Baron J. A prospective study of smoking and risk of prostate cancer. Int J Cancer 1996;67:764–8. [PubMed: 8824546]
10. Eichholzer M, Stahelin HB, Ludin E, Bernasconi F. Smoking, plasma vitamins C, E, retinol, and carotene, and fatal prostate cancer: seventeen-year follow-up of the prospective basel study. Prostate 1999;38:189–98. [PubMed: 10068343]
11. Hsing AW, McLaughlin JK, Hrubec Z, Blot WJ, Fraumeni JF Jr. Tobacco use and prostate cancer: 26-year follow-up of US veterans. Am J Epidemiol 1991;133:437–41. [PubMed: 2000853]
12. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ 1994;309:901–11. [PubMed: 7755693]
13. U.S. Department of Health and Human Services: Smoking and Health. Report of the Advisory Committee of the Surgeon General of the Public Health Service. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1964.
14. U.S. Department of Health and Human Services. Reducing the Health Consequences of Smoking - 25 Years of Progress: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1989.
15. Barrett-Connor E, Khaw KT. Cigarette smoking and increased endogenous estrogen levels in men. Am J Epidemiol 1987;126:187–92. [PubMed: 3605047]
16. Michnovicz JJ, Hershcopf RJ, Haley NJ, Bradlow HL, Fishman J. Cigarette smoking alters hepatic estrogen metabolism in men: implications for atherosclerosis. Metabolism 1989;38:537–41. [PubMed: 2725292]
17. Daniell HW. A worse prognosis for smokers with prostate cancer. J Urol 1995;154:153–7. [PubMed: 7776411]
18. Lawson T, Kolar C. Human prostate epithelial cells metabolize chemicals of dietary origin to mutagens. Cancer Lett 2002;175:141–6. [PubMed: 11741741]
19. Lin X, Tascilar M, Lee WH, Vles WJ, Lee BH, Veeraswamy R, Asgari K, Freije D, van Rees B, Gage WR, et al. GSTP1 CpG island hypermethylation is responsible for the absence of GSTP1 expression in human prostate cancer cells. Am J Pathol 2001;159:1815–26. [PubMed: 11696442]
20. Roberts WW, Platz EA, Walsh PC. Association of cigarette smoking with extraprostatic prostate cancer in young men. J Urol 2003;169:512–6. [PubMed: 12544299]

Table 1

Distribution of age, marital status, education, and smoking status in men in the 1963 and the 1975 Washington County, Maryland private censuses

	1963		1975	
	N	%	N	%
Age				
18–29	6,528	24.4	8,121	28.7
30–39	5,599	20.9	5,205	18.4
40–49	5,650	21.1	4,871	17.2
50–59	4,356	16.3	4,708	16.6
60–69	2,756	10.3	3,298	11.7
70 or older	1,921	7.2	2,089	7.4
Marital Status[1]				
Married	20,780	77.8	21,720	76.9
Widowed	928	3.5	748	2.7
Divorced or separated	902	3.4	1,113	3.9
Single	4,103	15.4	4,666	16.5
Education[2]				
Up to 8 years	9158	35.1	5,659	20.3
8–12 years	13016	49.9	15,895	57.0
13–16 years	3245	12.4	5,066	18.2
16 years or more	687	2.6	1,263	4.5
Smoking Status				
No active, no passive	3,884	14.5	5,782	20.4
Passive only	1,552	5.8	1,773	6.3
Former cigarette	5,079	18.9	7,649	27.0
Current cigarette	14,513	54.1	11,353	40.1
Pipe/cigar[3]	1,782	6.7	1,735	6.1

[1] marital status is missing for 97 men in the 1963 cohort and for 45 men in the 1975 cohort

[2] education is missing for 704 men in the 1963 cohort and for 409 men in the 1975 cohort

[3] assessed as ever smoked cigar or pipe in the 1963 census and as current cigar or pipe smoker in the 1975 census

Table 2

Risk of prostate cancer by smoking status in male participants of the Washington County, Maryland private censuses in 1963 and 1975

	1963				1975			
Smoking status	**Cases**	**Person-years**	**RR[1]**	**95% CI**	**Cases**	**Person-years**	**RR[1]**	**95% CI**
Total follow-up[2]								
Never smoker	34	51,474	1.00	ref.	94	89,789	1.00	ref.
Cigarette smoker								
Former	43	52,141	1.33	0.85–2.10	128	83,951	1.04	0.80–1.36
Current	45	146,956	1.00	0.63–1.59	85	124,340	0.98	0.73–1.33
Current, < 10 cig./d	5	21,166	0.52	0.20–1.33	10	10,129	1.12	0.58–2.15
Current, 10–19 cig./d	23	76,515	1.03	0.60–1.79	49	72,145	0.95	0.67–1.35
Current, 20+ cig./d	17	49,275	1.38	0.75–2.54	26	42,066	1.01	0.65–1.57
Cigar/pipe smoker[3]	25	17,117	1.25	0.75–2.10	44	22,431	1.19	0.83–1.70
First 10 years of follow-up[4]								
Never smoker	30	44,671	1.00	ref.	69	71,790	1.00	ref.
Cigarette smoker								
Former	40	44,220	1.44	0.89–2.32	96	68,951	1.03	0.76–1.40
Current	34	126,251	0.90	0.54–1.51	69	104,909	1.08	0.76–1.53
Current, < 10 cig./d	5	18,455	0.60	0.23–1.56	8	8,707	1.16	0.56–2.42
Current, 10–19 cig./d	15	65,749	0.81	0.43–1.53	38	61,278	0.99	0.66–1.48
Current, 20+ cig./d	14	42,047	1.38	0.71–2.67	23	34,924	1.25	0.77–2.03
Cigar/pipe smoker[3]	23	14,772	1.28	0.74–2.20	25	15,642	0.93	0.59–1.47

[1] RR = rate ratio; adjusted for age as a continuous variable

[2] Total follow-up was restricted to 1978 (1963 census; 15 years) and to 1994 (1975 census; 19 years), respectively

[3] Assessed as ever smoked cigar or pipe in the 1963 census and as current cigar or pipe smoker in the 1975 census

[4] Because weighting factors were applied for the probability of still being a resident in Washington County, MD, the majority of men had less than 10 years of follow-up, and the person-years for the first ten years of follow-up are close to total follow-up.

Table 3

Risk of prostate cancer death by smoking status in male participants of the Washington County, Maryland private censuses in 1963 and 1975

	1963				1975			
Smoking status	**Cases**	**Person-years**	**RR[1]**	**95% CI**	**Cases**	**Person-years**	**RR[1]**	**95% CI**
Total follow-up[2]								
Never smoker	56	156,970	1.00	ref.	44	165,800	1.00	ref.
Cigarette smoker								
Former	57	132,351	1.01	0.70–1.46	61	148,897	1.02	0.69–1.50
Current	104	403,335	0.93	0.67–1.29	59	235,864	1.25	0.84–1.87
Current, < 10 cig./d	21	63,601	1.11	0.67–1.84	5	17,971	1.12	0.44–2.82
Current, 10–19 cig./d	49	212,862	0.85	0.57–1.25	31	138,824	1.11	0.70–1.77
Current, 20+ cig./d	34	126,872	0.95	0.62–1.47	23	77,064	1.58	0.94–2.64
Cigar/pipe smoker[3]	23	42,184	0.94	0.58–1.54	20	33,450	1.31	0.77–2.22
First 10 years of follow-up								
Never smoker	7	50,667	1.00	ref.	5	71,971	1.00	ref.
Cigarette smoker								
Former	16	46,023	2.75	1.13–6.74	12	69,489	1.92	0.67–5.49
Current	16	135,882	2.38	0.94–5.99	8	106,476	2.21	0.69–7.08
Current, < 10 cig./d	4	20,885	2.37	0.69–8.14	1	8,886	2.25	0.26–19.4
Current, 10–19 cig./d	7	71,217	2.11	0.71–6.25	4	62,300	1.82	0.47–7.01
Current, 20+ cig./d	5	43,780	2.95	0.89–9.78	3	35,290	3.25	0.72–14.7
Cigar/pipe smoker[c]	4	15,558	0.90	0.26–3.07	1	15,654	0.49	0.06–4.20

[1] RR = rate ratio; adjusted for age as a continuous variable

[2] Total follow-up was not restricted and lasted until 2000 (men who were not diagnosed with cancer and were still alive were censored at the end of the study period in 2000)

[3] Assessed as ever smoked cigar or pipe in the 1963 census and as current cigar or pipe smoker in the 1975 census