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# Editorial

## Tobacco smoking and prostate cancer: Time for an appraisal

Worldwide prostate cancer is the fourth most common site for cancer incidence in men, and in developed countries it is the third site after lung and colon-rectum [1]. Considerable changes in incidence rates of prostate carcinoma have been observed in the USA, the European Union, and in most other developed countries, suggesting that an epidemic of this neoplasm occurred in the late 1980s or early 1990s, followed by a fall in rates. A critical appraisal of the descriptive epidemiology of prostate cancer indicates, however, that most trends were likely attributable to changes in diagnostic procedures (mainly, the introduction of prostate-specific antigen–PSA–blood test), rather than to substantial changes in risk factor exposure [2].

In any case, the descriptive epidemiology of prostate cancer is inconsistent with a major role of tobacco in prostate cancer risk, given its time trends and geographic pattern. Thus, while mortality rates from lung and other tobacco-related neoplasms have substantially changed in various countries following the spread of cigarette smoking in subsequent generations, only minor long-term changes have been observed in prostatic cancer mortality rates.

Nonetheless, a possible relation between prostate cancer and cigarette smoking has been considered in several studies [3–59]. Among these, only two case-control [16, 17] and four prospective studies [42, 46–50, 53] showed a positive relation between prostate cancer and tobacco smoking. This relationship, if real, may be mediated by hormonal factors, since male cigarette smokers have elevated levels of serum testosterone and androstenedione [60]. However, one review on the health effects of cigarette smoking [61] and two other on major risk factors for prostate cancer [62–63], did not support the association between cigarette smoking and increased risk for prostate cancer.

The main results from case-control studies are given in Table 1. Among the 30 case-control studies that examined the role of cigarette smoking on prostate cancer [3–34], only two reported a positive association [16, 17]. The study by Honda et al. [17], based on 216 cases and 212 controls, showed a moderate positive relation between prostate cancer and cigarette smoking (smokers vs. nonsmokers: RR = 1.9, 95% confidence interval (95% CI): 1.2–3.0) and a significant direct trend only in the highest level of smoking duration. The study by Schuman et al. [16] also showed some association with cigarette smoking when comparison was made with population controls only, but it was too small (40 cases) to be informative. Furthermore, a study of 345 cases and 1346 hospital controls from the Netherlands [22] found a direct association with ever smoking, but no dose- nor duration-risk relationship. Moreover, these results also contrast with other case-control studies [6, 8, 9, 14, 15, 18, 19, 23, 24, 29] which, using population controls, did not show any meaningful association between tobacco smoking and prostate cancer. However, a large Canadian population-based case-control study [32] found a modest and inconsistent inverse association with various measures of cigarette smoking.

Thus, most case-control studies found no association between smoking and prostate cancer, with a few reporting direct or other inverse associations, which appear to be attributable to mere chance, in the absence of any causal association.

Among 22 prospective studies [35–59], four [42, 46–50, 53] showed some positive relation with cigarette smoking (Table 2). Hsing et al. [49] and McLaughlin et al. [50] in the US Veterans Cohort Study found a significantly elevated relative risk among cigarette smokers (RR = 1.2; 95% CI: 1.1–1.3), particularly among heavy smokers (OR = 1.5 in smokers of 40 or more cigarettes per day compared with nonsmokers). Hsing et al. [42] in a report on a Lutheran Brotherhood cohort study, reported significantly elevated relative risks among persons who smoked any type of tobacco (RR = 1.8; 95% CI: 1.1–2.9), as well as among users of smokeless tobacco (RR = 2.1; 95% CI: 1.1–4.1). However, no clear dose-response relation was found. Likewise, the data of the Cancer Prevention Study II (CPSII, 53) showed an elevated risk (RR = 1.3; 95% CI, 1.2–1.6) of fatal prostate cancer in cigarette smokers, with a stronger association below age 60, but no trend in risk with number of cigarettes smoked nor duration of smoking. The conclusion was that smoking may adversely affect survival in prostatic cancer patients [53]. Positive results came from the US Kaiser Permanente Study [46], based on 238 cases.

Another prospective study from Norway [59] found a weak positive association with number of cigarettes smoked, and a cohort study of Iowa men [55, 56], including only about 100 prostate cancer cases, showed a nonsignificant association with number of cigarettes. Likewise, the MRFIT [51] cohort showed a significant excess risk for smokers vs. nonsmokers, in the absence of any dose-risk relation (i.e., RR was 1.5 for smokers of $< 15$ cigarettes/day, but 1.2 for smokers of $> 45$ cigarettes/day).

In contrast, no association between smoking and prostate cancer was evident from the British Physicians [45], the US Health Professionals' [57] and the Physicians' Health Study [58].

*Table 1.* Summary of results of case-control studies on prostate cancer in relation to cigarette smoking.

| Investigator(s) [references] | Location | No. of subjects | Major findings |
|---|---|---|---|
| Schwartz et al., 1961 [3] | Paris, France | 139 cases<br>139 hospital controls | No association, 79% and 73% of smokers among cases and controls, respectively |
| Wynder et al., 1971 [4] | New York, US | 300 cases<br>400 hospital controls | No association; 40% and 39% of cigarettes smokers among cases and controls, respectively |
| Kolonel and Winkelstein, 1977 [5] | New York, US | 176 cases<br>269 hospital controls | No significant association[a]; ever-smokers: OR = 1.1 (non-cancer controls), OR = 1.0 (cancer controls) |
| Williams and Horn, 1977 [6] | US (Third Nat. Cancer Controls Survey) | 257 cases<br>1116 population controls | No association; no. of cigarettes smoked: 1–400/yr, OR = 0.7; 401–800/yr, OR = 0.7; > 800/yr, OR = 0.9 |
| Nijima and Koiso, 1980 [7] | Japan | 187 cases<br>200 hospital controls | No association |
| Ross et al., 1987 [8] | Los Angeles, US | 284 cases (142 blacks and 142 whites)<br>284 population controls (142 blacks and 142 whites) | No association[a], ever-smokers: whites, RR = 1.1; blacks, RR = 0.9 |
| Mishina et al., 1985 [9] | Kyoto, Japan | 111 cases<br>100 population controls | No significant association[a]; ever-smokers· RR = 1.6 |
| Checkoway et al , 1987 [10] | Chapel Hill, US | 40 cases<br>64 hospital controls | No association |
| Yu et al., 1988 [11] | US | 1162 cases (989 whites and 161 blacks)<br>3124 hospital controls (2791 whites and 320 blacks) | No significant association[a];<br>whites. ex-smokers: OR = 0.9; current smokers: OR = 1.0;<br>blacks: ex-smokers: OR = 1.4; current smokers: OR = 1.7 |
| Newell et al , 1989 [12] | Houston, US | 103 cases<br>220 hospital controls | No association |
| Oishi et al , 1989 [13] | Kyoto, Japan | 117 cases<br>296 hospital controls | No significant association; current smokers: OR = 0.6; former smokers: OR = 1.4 |
| Slattery et al., 1990 [14] | Utah, U.S. | 385 cases<br>679 population controls | No association |
| Fincham et al , 1990 [15] | Alberta, Canada | 382 cases<br>625 population controls | No association[a], ex-smokers: RR = 0.8; current smokers: RR = 0.9 |
| Schuman et al., 1977 [16] | Minneapolis, US | 40 cases<br>43 hospital<br>35 neighborhood controls | Direct association, when neighborhood, but not hospital controls, were used |
| Honda et al., 1986 [17] | California, US | 216 cases<br>212 population controls | Ever smokers: RR = 1.9, years of smoking: > 40, RR = 2.6 |
| Slattery et al., 1993 [18], Elgany et al., 1990 [19] | Utah, US | 720 cases<br>1364 population controls | 57% and 58% of ever-smokers among cases and controls |
| Talamini et al., 1993 [20]; Tavani et al., 1994 [21] | Northern Italy | 281 cases<br>599 hospital controls | No significant association[a]; ever-smokers. OR = 0.8 |
| Van der Gulden et al., 1994 [22] | The Netherlands | 345 cases<br>1346 hospital controls | Significant direct association; ever-smokers: OR = 2.1; no relation with amount, duration or age started smoking |
| Hayes et al., 1994 [23] | Atlanta, Detroit, New Yersey, US | 981 cases (502 whites, 479 blacks)<br>1315 population controls (721 whites, 594 blacks) | Whites· current smokers: OR = 1.2; former smokers: OR = 1.2<br>Blacks. current smokers. OR = 1.0; former smokers: RR = 1 1 |
| Siemiatycki et al., 1995 [24] | Montreal, Canada | 449 hospital cases<br>1266 population controls | No significant association[a]; ever-smokers OR = 1.0 |
| De Stefani et al., 1995 [25] | Uruguay | 156 cases<br>302 hospital (cancer) controls | No significant association[a]; ever-smokers: OR = 0.7; ex-smokers: OR = 0.6; current OR = 0.8 |
| Ilic et al , 1996 [26] | Serbia, Yugoslavia | 101 cases<br>202 hospital controls | No significant difference in smoking habits or in the number or type of smoking |

*Table 1.* Continued.

| Investigator(s) [references] | Location | No. of subjects | Major findings |
|---|---|---|---|
| Andersson et al., 1996 [27] | Sweden | 256 cases<br>252 population controls | Current-smokers OR = 1.8; no dose-response trend |
| Pawlega et al., 1996 [28] | Poland | 76 cases<br>152 controls | No association |
| Key et al., 1997 [29] | UK | 328 cases<br>328 population controls | No significant association, current smokers: OR = 1.1; former-smokers: OR = 1.1 |
| Lumey et al., 1997 [30] | US | 1097 cases<br>3250 hospital controls | No association; current smokers: OR = 0.9; ex-smokers: OR = 0.9, No dose-response trend |
| Rohan et al., 1997 [31] | Canada | 408 cases<br>407 population controls | Direct association; current-smokers: OR = 1.4, ex-smokers. OR = 1.7 |
| Villeneuve et al., 1999 [32] | Canada | 1623 cases<br>1623 population controls | Nonsignificant inverse association |
| Sung et al., 1999 [33] | Taiwan | 90 cases<br>180 hospital controls | 46% and 40% of smokers in cases and controls, respectively; ever-smokers: OR = 1.3 |
| Giles et al., 2001 [34] | Australia | 1476 cases<br>1409 population controls | No association[a]; ever-smoker: OR = 1.0, ex-smokers OR = 1 0; current smokers: OR = 0 8 |

Abbreviations: RR – relative risk; OR – odds ratio.
[a] Never-smokers as reference category

*Table 2.* Summary of results of cohort studies on prostate cancer in relation to cigarette smoking.

| Investigator(s) [reference] | Location | No. of subjects | Major findings |
|---|---|---|---|
| Hammond, 1966 [35] | US | 440,558 (319 cases) | No association |
| Weir and Dunn, 1970 [36] | California, US | 68,153 (37 cases) | No association[a]; ever-smokers: RR = 0 8, < 1/2 pk/day, RR = 0.6, 1 pk/day, RR = 1.0, > 1 pk/day, RR = 0.8 |
| Hirayama, 1979 [37] | Japan | 122,261 (63 cases) | No association; age-standardized death rate per 100,000, among non-smokers (6 1), ex-smokers (3 7), current smokers (5.8) |
| Whittemore et al., 1985 [38] | US (college alumni) | 47,271 (243 cases) | No association |
| Carstensen et al., 1987 [39] | Sweden | 25,129 (193 cases) | No association[a], ex-smokers: RR = 1.0; no. cigarettes smoked. 1–7/day, RR = 1.1; 8–15/day, RR = 0 8; > 15/day, RR = 0.9 |
| Severson et al., 1989 [40] | Honolulu, Japan | 7,999 (174 cases) | No association[a]; ex-smokers, RR = 0.9; current smokers RR = 0.9 |
| Mills et al., 1989 [41] | California, US | 14,000 (180 cases) | No association[a]; ex-smokers, RR = 1 2, current smokers: RR = 0 5 |
| Hsing et al., 1990 [42] | Minnesota, US | 17,633 (149 cases) | Positive association[a]; ever used any form of tobacco· RR = 1 8; current smokers, RR = 2 0 |
| Ross et al., 1990 [43] | California, US | 5105 (138 cases) | No association[a]; current smokers: RR = 0 9; former smokers: RR = 0.8 |
| Mills and Beeson, 1992 [44] | California, US (7th Day Adventists) | 14,000 (180 cases) | No association, current smokers: RR = 1.0; no relation with amount or duration of smoking |
| Doll et al., 1994 [45] | UK (physicians) | 34,440 (568 cases) | RR = 0 8, 1 1, 1.2 in subsequent levels of smoking |
| Hiatt et al., 1994 [46] | California, US (Kaiser perman ) | 43,432 (238 cases) | Positive association; compared to never-smokers, ≤ 20 cig/day, RR = 1.0; > 20 cig/day, RR = 1.9 (95% CI. 1.2–3 1) |
| Kahn, 1966 [47]<br>Rogot and Murray, 1980 [48]<br>Hsing et al., 1991 [49] | US (veterans) | 293,916 (4,607 cases) | Ex-smokers RR = 1 1; current smokers, RR = 1 2; 10–20/day, RR = 1 2; 21–39/day, RR = 1.2, > 39/day, RR = 1.5 |
| McLaughlin et al., 1995 [50] | US (veterans) | 293,916 (3,124 deaths) | Positive association[a], ex-smokers· RR = 1 1; 10–20 cig/day, RR = 1.2; 21–39 cig/day, RR = 1 2; 21–39 cig/day, RR = 1.2; ≥ 40 cig/day, RR = 1.5 |

*Table 2.* Continued.

| Investigator(s) [reference] | Location | No. of subjects | Major findings |
|---|---|---|---|
| Coughlin et al., 1995 [51] | US (MRFIT) | 348,874 (826 cases) | Positive association, 1–15 cig/day, RR = 1 5, 16–25 cig/day, RR = 1 3, 26–35 cig/day, RR = 1 2; 36–45 cig/day, RR = 1 5; > 45 cig/day, RR = 1.2 |
| Adami et al , 1996 [52] | Sweden | 135,006 (2,368 cases) | Current-smokers: RR = 1.1; ex-smokers: RR = 1 1; no trend with amount or duration of smoking |
| Rodriguez et al., 1996 [53] | US (Cancer Prevention Study II) | 450,279 (1,748) | Positive association with current smoking for fatal cancers, ever-smokers· RR = 1.0, current cig only smokers: RR = 1.3, former cig only smokers: RR = 1 0; no trend with amount of duration of smoking |
| Cerhan et al., 1997 [54] | Iowa, US | 1,050 (71 cases) | 63% and 58% ever-smokers among cases and controls; current, < 20 cig/day, RR = 2 0; current, ⩽ 20 cig/day, RR = 2.9; significant dose-dependent trend |
| Parker et al., 1999 [55] | Iowa, US | 1,117 (81 cases) | Former-smokers: RR = 1 3, current, < 20 cig/day, RR = 1.7, current, ⩽ 20 cig/day, RR = 1.9 |
| Putnam et al., 2000 [56] | Iowa, US | 1,572 (101 cases) | Non-significant association; former-smokers: RR = 1.4; current, < 20 cig/day, RR = 1.3; current, ⩽ 20 cig/day, RR = 1.6 |
| Giovannucci et al , 1999 [57] | US (Health professionals) | 51,529 (1,369 cases) | No association[a]; current smokers: RR = 1.1; impact of recent use on occurrence of fata cancer (RR = 1 6) |
| Lotufo et al., 2000 [58] | US (Physicians' Health study) | 22,071 (996) cases) | No association[a]; ex-smokers: RR = 1.1; current < 20 cig/day, RR = 1.1; current, ⩽ 20 cig/day, RR = 1.1; no dose- or duration-dependent trend |
| Lund Nilsen et al., 2000 [59] | Norway | 22,895 | RR = 0 8, 1 1, 1 4, 1 3 for subsequent levels of cigarette smoking |

Abbreviations: RR – relative risk, OR – odds ratio.
[a] Never-smokers as reference category.

This pattern of risk would suggest that the relation between smoking and prostate cancer diagnosis or death may not be causal, but attributable to other socioeconomic or lifestyle correlates of smoking [60–64], which are likely to be less relevant in studies conducted in health-conscious populations with, for example, doctors or health professionals. A major problem of cohort studies, in fact, is often the limited number of covariates available in order to allow for potential confounding.

The report by Giles et al. [34], based on a uniquely large case-control study, provides further evidence on an absence of excess risk of prostate cancer among current or former smokers, including those who smoked the highest number of cigarettes for the longest period of time. There is also a lack of material influence of smoking on prostate cancer in younger or elderly men, with early or advanced, or moderate or high grade neoplasms.

Together with the available evidence on this issue, the results from this study provide, therefore, definite evidence that cigarette smoking is not a relevant risk factor for prostate cancer, even after a long latency period. The issue of a modest association remains open to debate, but it is unclear whether such a modest association can be investigated in observational epidemiological studies, in consideration also of the need for careful allowance for confounding, since some differences in other factors (including dietary, socioeconomic, or other) may account for the apparent inconsistencies observed across studies [65, 66].

These cautions notwithstanding, it is now clear, in conclusion, that tobacco smoking is not a relevant risk factor for prostate cancer.

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