

Cigarette Smoking and Testicular Cancer

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Abstract

The purpose of this study was to determine the relation between testicular cancer and cigarette smoking. Data were collected between 1995 and 1996 in Ontario, Canada, as part of the Enhanced Cancer Surveillance Study. Pack-years and years of smoking were examined among all subjects (212 cases and 252 controls) and former and current smokers. Years since quitting and age at smoking initiation were examined among former and current smokers only. Independent of smoking status, significant associations were noted among those who smoked between 12 and 24 pack-years [odds ratio (OR) = 1.96 (95% confidence interval (CI): 1.04–3.69), relative to nonsmokers] or greater [>24 pack-years, OR = 2.31 (95% CI: 1.12–4.77), relative to nonsmokers], and among those who smoked >21 years [OR = 3.18 (95% CI: 1.32–7.64), relative to nonsmokers]. Quitting smoking was not found to result in a reduction of risk. No association was observed for smoking at adolescence relative to a later period. Results from the study suggest that cigarette smoking exerts an adverse influence on testicular cancer risk that is not mitigated by smoking cessation and not altered by age at initiation.

Introduction

Although tobacco smoking is commonly considered to be an important risk factor for many cancers, it is not clear if risk of testicular cancer is affected similarly. The possibility that smoking may be harmful in relation to testicular cancer is plausible: cigarette smoke contains known carcinogens such as arsenic (1). Furthermore, smoking may modify sex hormones, which are implicated in the onset and/or progression of testicular cancer (2). Assuming an adverse relationship between testicular cancer and smoking, it is expected that former smokers will have decreased risks of testicular cancer relative to current smokers, a hypothesis in keeping with observations for other cancers such as lung (see, for example, Ref. 3). We additionally expect early age of smoking initiation to be ad-

versely associated with testicular cancer risk. Only two studies (4, 5) have suggested an adverse association between smoking and testicular cancer, with the remainder of studies reporting no association (6–9). Of these studies, only one (7) evaluated more than one measure of smoking; only one (4) has examined age at smoking initiation; and only one has examined the effect of quitting smoking (5). None has considered physical activity as a confounder. There is a clear need for a better understanding of the relation between testicular cancer and smoking.

Certainly, additional investigation into a modifiable lifestyle factor is of importance: testicular cancer, although rare relative to other cancers, is the most common cancer among younger men (10). Because of this age distribution and because in Ontario 31% of males ages 15–24 years are current smokers (11), findings of increased risk may have important public health implications.

Materials and Methods

The data were derived from the Enhanced Cancer Surveillance (ECS) study, a national case-control study that examined a number of primary cancer sites including the testis. Subjects were aged between 20 and 74 years of age. Ontario cases were selected from a review of pathology reports received at the Ontario Cancer Registry; those with a new germ cell testicular cancer (12, 13) diagnosed between January 1, 1995, and December 31, 1996, were included in the Enhanced Cancer Surveillance study. The control sampling frame was based on the Ontario Ministry of Revenue Property Assessment databases, which consist of two main files: a list of all residents of Ontario and a list of all property addresses. The list of residents contains surnames, given names, and year and month of birth. From these name lists, files were assembled that contained the names of residents of Ontario by sex and 5-year age groups. Because controls were selected for age matching to a number of cancer sites, it was necessary to further frequency match within appropriate age strata for the testicular cancer cases in an approximate 1:1 ratio.

Questionnaires were mailed to controls after sampling had occurred and to cases once physician consent and an address had been obtained. Postcard reminders were mailed 1–2 weeks after the initial mailing, followed by another questionnaire and a reminder letter in the event of a nonresponse; continued nonresponse 6 weeks after the first questionnaire was mailed resulted in a telephone call. After receipt of the questionnaire, in the event of substantial or key missing information, blinded callbacks were performed. Seventy-six percent of questionnaires sent to cases with testicular cancer were returned, a response rate representing 212 cases, whereas the 251 controls represented a response rate of 64%.

Assessment of Smoking Habits. For those smoking a lifetime minimum of 100 cigarettes, a number of smoking characteristics were assessed, including average number of cigarettes smoked daily, age at initiation, and, if applicable, age at quitting (Appendix A). Those who had not ever smoked either at least 100 cigarettes, a pipe, or a cigar were considered to be non-

Received 4/24/03; revised 9/15/03; accepted 9/18/03.

Grant support: Action Plan on Health and the Environment, Laboratory Centre for Disease Control of Health Canada.

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smokers. Assuming 20 cigarettes/package, 1 pack-year was estimated to be 7305 cigarettes. The smoking of one pipe was assumed to be equivalent to 5 cigarettes (8); the respective pack-years of those who smoked both cigarettes and pipes were summed. Information on current smoking status was not available for pipe smokers; those who smoked a pipe exclusively were excluded from the analysis, but if they were both cigarette and pipe smokers, information on smoking status for cigarettes was used. Among smokers, only 7 were exclusively pipe smokers. No information was obtained on the type of tobacco or cigarettes.

Subjects who indicated that they no longer smoked were considered to be former smokers. The number of years that one had quit was calculated as the difference between current age and the age at quitting. Reasons for quitting such as poor health were not obtained. Because of the possibility that smokers may have quit in response to a diagnosis of cancer, smokers were considered to be former smokers only if they had quit ≥ 2 years ago. The number of self-reported former smokers affected by this restriction was 28.

To examine the effect of age at smoking initiation, a cut point, set at 16 years of age, was established on both biological and statistical grounds: the peak surge in sex hormones is thought to be completed by ~ 17 years of age, after which, adult levels of sex hormones persist (14), and a cut point much past this age would have left too few subjects for analysis in the older age group.

Assessment of Confounders. Because physical activity at adolescence has been found to adversely affect testicular cancer risk (15) and may be associated with smoking habits (16), frequency of adolescent physical activity was summed for both moderate and strenuous recreational activity, and quartiles were formed; the variable was modeled as continuous categorical (*i.e.*, with the assumption of a common slope). Information on self-reported body mass index [weight (kg)/height (m^2)] and educational level was also assessed. Body mass index was formulated into quartiles based on the control distribution, and educational level was categorized according to thresholds thought to be most likely correlated with socioeconomic status (Table 1). Body mass index was modeled as a categorical variable with the assumption of different slopes and educational level as continuous categorical. Age, which was adjusted for in all analyses, was modeled as a continuous categorical variable because no improvement in log-likelihood was observed when it was modeled only as a categorical variable as evaluated in bivariate analyses of age and both of pack-years and years of smoking modeled continuously.

Statistical Analysis. Unconditional logistic regression was performed for the desired models. For all models, we compared the odds ratio (OR) of the continuous exposure with and without the potential confounder; a variable was considered to be a confounder if an OR change of $\geq 10\%$ was observed for the smoking variable upon the potential confounder's exclusion from the complete model. If a variable was not considered to be a confounder, it was nonetheless retained unless a decrement in precision of $> 10\%$, as judged by the width of the CI associated with the OR of interest, was observed. Depending upon the model, multiplicative interaction terms—chosen on the basis of biological plausibility—were examined; for models with multiple interaction terms, a global test for interactions was performed such that each individual term was examined further only if the likelihood ratio test indicated a meaningful—approaching a P of 0.10—difference between models with and without interaction terms (17).

Table 1 Frequency distribution of cases and controls by age, education, body mass index, and physical activity, Ontario, Canada: 1995–1996

Variable	No. (%) cases	No (%) controls
Age group (yrs)		
20–24	23 (10.8)	26 (10.3)
25–29	28 (13.2)	38 (15.1)
30–34	47 (22.2)	46 (18.3)
35–39	45 (21.2)	45 (17.9)
40–44	29 (13.6)	41 (16.3)
45–49	19 (9.0)	26 (10.4)
50–54	9 (4.2)	11 (4.4)
55+	12 (5.7)	18 (7.2)
Education		
\leq Grade 11	38 (18.1)	51 (20.7)
$>$ Grade 11, no postsecondary	39 (18.6)	52 (21.1)
$>$ Grade 11, some postsecondary	133 (63.3)	143 (58.1)
BMI (kg/m^2)		
< 22.7	44 (20.8)	63 (25.3)
22.8–25.0	50 (23.6)	66 (26.5)
25.1–27.6	63 (29.7)	61 (24.5)
> 27.6	55 (25.9)	59 (23.7)
Physical activity ^a		
≤ 1	41 (21.5)	44 (20.1)
> 1 to ≤ 3	43 (22.5)	58 (26.7)
> 3 to ≤ 7.5	41 (21.5)	46 (21.0)
> 7.5	66 (34.6)	71 (32.4)

^a Summed moderate and strenuous activity, times/week.

Results

Table 1 presents the study sample by age and education. As can be seen, cases (and by design, controls) are highly skewed toward the younger age groups. The majority of cases and controls have attained at least some postsecondary education.

Because the relationship between pack-years and risk of disease has sometimes been found to be logarithmic (see, for example, Ref. 18), a logarithmic model [$\log(\text{pack-years} + 0.5)$] with its linear counterpart were fit. Because little difference was found in the goodness of fit, the simpler linear model was chosen. Physical activity did not confound the association with disease and continuous pack-years among all smokers or within strata (former and current smokers). The continuous model was also used to evaluate interactions with pack-years and both of current body mass index and adolescent physical activity; no interactions were found to approach P of 0.10.

A less stringent model was then formulated in which pack-years were categorized in quartiles that were based on the distribution of controls who had ever smoked (Table 2). Unstratified analysis—where stratified refers to analysis by smoking status—revealed moderately elevated estimates at all levels of pack-years; the association between cancer and pack-years was most definitive at ≥ 12 pack-years [> 12 to ≤ 24 pack-years, OR = 1.96 (95% CI: 1.04–3.69); > 24 pack-years, OR = 2.31 (95% CI: 1.12–4.77)]. The estimates of the ORs exhibited a monotonic increase with sequential categories of pack-years. When stratified by smoking status, only former smokers demonstrated a statistically significant association, observed at > 24 pack-years, and in general, estimates among former smokers tended toward somewhat greater statistical significance and magnitude than those of current smokers.

We next examined years of smoking (Table 2). Among all smokers, elevated estimates were observed similar to those observed with pack-years. The strongest relationship was at 21 years in which a statistically significant effect of relatively large magnitude was observed [OR = 3.18, (95% CI: 1.32–7.64)].

Stratified analysis revealed that both former and current smokers also exhibited their strongest relationship at >21 years, although this was significant only for former smokers.

Because of the suggestion of differential risk between former and current smokers, a formal comparison between former and current smokers was performed for both pack-years and years smoked. Logistic regression was used as follows: current smokers at a given level of pack-years or years smoked were coded as the referent category and entered into a model with former smokers, where the only relevant comparison was former and current smokers at the same level. No comparison achieved statistical significance (data not shown).

To explore further the association between quitting smoking and risk of disease, we examined years since quitting among ever smokers (former and current). We present results for the categorical model in Table 3. Relative to current smokers, there was no reduction in risk associated with quitting smoking. The interaction between pack-years and years since quitting was not found to approach a significant likelihood ratio as judged by *P* of 0.10.

Finally, the importance of age at smoking initiation among

Table 2 Adjusted^a odds ratio estimates and 95% confidence intervals for pack-years and years of smoking among all subjects and by smoking status, Ontario, Canada, 1995–1996

Pack-years	Cases/controls	Odds ratio	95% confidence interval
All subjects			
0 (nonsmoker)	70/112	1.00	
>0 to ≤5	31/34	1.56	(0.87–2.82)
>5 to ≤12	33/34	1.61	(0.89–2.92)
>12 to ≤24	34/32	1.96	(1.04–3.69)
>24	30/32	2.31	(1.12–4.77)
Current smokers			
0 (nonsmoker)	70/112	1.00	
>0 to ≤5	12/14	1.24	(0.53–2.92)
>5 to ≤12	20/20	1.79	(0.74–3.04)
>12 to ≤24	22/22	1.50	(0.87–3.67)
>24	18/21	1.86	(0.82–4.22)
Former smokers			
0 (nonsmoker)	70/112	1.00	
>0 to ≤5	22/17	1.98	(0.92–4.25)
>5 to ≤12	13/14	2.23	(0.90–5.51)
>12 to ≤24	12/10	2.59	(0.92–6.79)
>24	12/11	3.30	(1.03–10.57)
Years of smoking			
All subjects			
0 (nonsmoker)	70/112	1.00	
>0 to ≤10	38/41	1.67	(0.90–3.18)
>10 to ≤15	22/26	1.52	(0.71–3.24)
>15 to ≤21	31/30	1.90	(0.89–4.05)
>21	31/36	3.18	(1.32–7.64)
Current smokers			
0 (nonsmoker)	70/112	1.00	
>0 to ≤10	16/18	1.21	(0.49–3.01)
>10 to ≤15	12/14	1.26	(0.45–3.49)
>15 to ≤21	20/21	1.67	(0.61–4.57)
>21	24/24	2.73	(0.85–8.75)
Former smokers			
0 (nonsmoker)	70/112	1.00	
>0 to ≤10	22/23	1.53	(0.67–3.52)
>10 to ≤15	10/12	1.92	(0.63–5.88)
>15 to ≤21	11/9	2.36	(0.70–7.92)
>21	12/7	5.39	(1.19–24.46)

^a Adjusted for education, age, combined moderate and strenuous recreational physical activity at adolescence, body mass index, and for years smoked, average number of cigarettes smoked/day (continuous).

Table 3 Adjusted^a odds ratio estimates and 95% confidence intervals for years since quitting smoking among ever smokers, Ontario, Canada, 1995–1996

Year since quitting	Cases/controls	Odds ratio	95% confidence interval
0 to ≤2 (current smokers)	52/72	1.00	
>2 to ≤7	37/14	1.95	(0.80–4.80)
>7 to ≤13	15/13	1.43	(0.60–3.42)
>13 to ≤20	14/14	1.33	(0.54–3.28)
≥20	14/17	1.22	(0.40–3.69)

^a Adjusted for age, education, body mass index, combined moderate and strenuous recreational physical activity at adolescence, pack-years (continuous).

Table 4 Adjusted^a odds ratio estimates and 95% confidence intervals for age at smoking initiation among ever smokers (former and current) and by smoking status, Ontario, Canada, 1995–1996

Age (yrs) at smoking initiation	Cases/controls	Odds ratio	95% confidence interval
Ever smoked			
>16	49/45	1.00	
≤16	85/87	0.91	(0.52–1.60)
Former smokers			
>16	22/19	1.00	
≤16	38/34	1.39	(0.50–3.85)
Current smokers			
>16	27/26	1.00	
≤16	47/52	0.69	(0.32–1.49)

^a Adjusted for age, education, body mass index, combined moderate and strenuous recreational physical activity at adolescence, pack-years (continuous), and for former smokers and ever smoked, years since quitting (categorical).

ever (current and former) smokers is shown in Table 4. There was no effect of initiation age and subsequent disease risk as evaluated in either unstratified or stratified analyses. Interaction terms between age at starting to smoke and both of adolescent physical activity or current body mass index did not approach a *P* of 10% as judged by the likelihood ratio test.

Discussion

We observed a moderate positive association between smoking and risk of testicular cancer. Although smoking to any degree was suggestive of an increased risk, the strongest—large effect size and statistically significant—results were observed, independent of smoking status, among those who smoked between 12 and 24 pack-years [OR = 1.96 (95% CI: 1.04–3.69)] or more [>24 pack-years, OR = 2.31 (95% CI 1.12–4.77)] and among those who smoked about ≥21 years [OR = 3.18 (95% CI: 1.32–7.64; Table 2)]. Although levels of smoking less than this were not statistically significant, examination of the effect estimates and CIs, particularly for pack-years, suggests a dose response relationship.

Modest but suggestive associations between testicular cancer and smoking have been noted in two large population based studies. The United Kingdom Testicular Cancer Group (4) reported a slight elevation in risk among ever smokers relative to never smokers [OR = 1.18 (95% CI: 0.96–1.46)]. No meaningful relationship was observed with smoking intensity, although for example, at the category of 10–19, an OR of 1.28 (95% CI: 0.98–1.66) was obtained. Smoking intensity was calculated by multiplying the average number of cigarettes smoked/day by the number of years smoked and then dividing by (the subjects' age minus 13 years). The impact of this

averaging of intensity is not clear, although cumulative smoking exposure would appear to be a more important measure; such a measure is likely to additionally minimize the contribution of smoking started at later relative to earlier ages. Gallagher *et al.* (5), in their case-control study of 510 cases, noted an association suggestive of increased risk of testicular cancer among those with an 11+ pack-year history [OR = 1.4 (95% CI: 1.0–1.8), relative to nonsmokers], a threshold in accordance with our observed stronger association at ≥ 12 pack-years. Other studies have not found an association (6–9); these include a study by Henderson *et al.* (6) in which only an ever smoked *versus* never smoked relative risk was reported and a study by Coldman *et al.* (7) in which the data were not shown. Our analysis does not suggest that failure to account for physical activity confounded results.

The synthesis of our results suggests that smoking about a pack a day for ~ 20 years increases one's risk of testicular cancer ~ 2 -fold. In Ontario, $\sim 25\%$ of males ages ≥ 25 years are classified as current smokers, with an average of 18 cigarettes—almost a pack—smoked/day (11). Assuming that this habit continues to a cumulative time period of ~ 20 years, we then calculate the population attributable risk among current smokers > 25 years to be anywhere from 20 to 27% at an OR of 2 and 2.5, respectively. This compares, for example, with a calculated population attributable risk of 26% among white smokers who developed pancreatic cancer (19) but is considerably less than the 90% attributable risk associated with lung cancer and smoking (20).

Although the testes are a distant site from the source of smoke inhalation, many other such remote sites have been found to be associated with smoking, including kidneys (21). Indeed, with respect to the relation between other cancers and smoking, the observed increased risk compares with the approximate 2-fold risk among ever-smokers observed in, for example, cancer of the kidney or pancreas (21). It is likely that an increased risk of testicular cancer among smokers can be attributable at least in part to hazards associated traditionally with smoking and cancer such as chemically induced genetic mutation (22) or impairment of immune function (23). A study that investigated the relationship between testicular cancer and glutathione *S*-transferase $\mu 1$ deficiency yielded no evidence of an association (24) where the enzyme is involved in the detoxification of activated metabolites of carcinogens and its deficiency is thought to predispose to, for example, cancer of the esophagus, especially among smokers (25). It is possible that, as is suggested with the protective association observed in endometrial cancer (26), smoking might modulate sex hormone levels, which, because of the evidence linking these hormones with testicular cancer (2), would in turn affect one's risk. As an example, higher testosterone (27–29) or androstenedione (29, 30) levels—protective prenatally but perhaps later serving as a carcinoma *in situ* furthering second hit (2)—have been found in smokers relative to nonsmokers, although others have reported no differences (31–35). Elevated levels of gonadotropins, including lutenizing hormone and follicle-stimulating hormone, may also be important: those with Kallmann's syndrome, for example, who have insufficient gonadotropin secretion almost never develop testicular cancer (2). Yardimci *et al.* (36), however, found no change in levels of lutenizing hormone and follicle-stimulating hormone among rats exposed to smoke. Although a protective antiestrogenic effect of smoking is sometimes suggested in studies of breast and ovarian cancer (37), there is evidence that estrogens may be positively affected by smoking (38, 39). Although raised maternal estrogen levels may have an adverse prenatal association (40), the postnatal

association is unknown, although in adult mice and hamsters, chronic exposure to exogenous estrogenic compounds has been shown to promote cancer of the testes (41).

Various types of testicular tumors, broadly labeled as seminomas and nonseminomas, may be differentially associated with hormonal and nonhormonal stimuli: power restrictions precluded separate analyses in this study. Thus far, no risk factor has been noted to be consistently associated by histological type (5, 8, 42, 43). Another possible limitation is the lack of adjustment for race or ethnicity. Blacks have consistently been shown to have a lower incidence to testicular cancer relative to whites (see, for example, Ref. 43), and Asians may have a lower incidence than those of Western European background (5); none of the above associations has been adjusted for socioeconomic status, and it is not clear whether the above findings represent established residents or recent immigrants. At least one study has found that adolescent whites are more likely than blacks to smoke (44). If there were a greater proportion of nonwhite controls than cases and they were less likely to smoke, then this may have inflated our OR estimates. We note that we did not include information on cryptorchidism, an established risk factor for testicular cancer. As the Enhanced Cancer Surveillance Study was not designed specifically to investigate testicular cancer, risk factors particular to this cancer were not inquired about. We point out, however, that the studies to have adjusted for it have not found much of an alteration in ORs (4, 5, 7). Certainly, we cannot think of a plausible association between undescended testes and smoking behavior, a necessary condition of a confounder.

Although evidence of an association with testicular cancer and late onset puberty (45) and frequent physical activity in one's teens (15) support the notion of adolescence as a particularly susceptible period, we did not observe an association between age at smoking initiation and risk of disease. The United Kingdom Testicular Cancer Group (4) also found no association with age at starting to smoke, although their cut points are unknown. The lack of an observed effect in adolescence in this study may be attributable to the limited exposure distribution among our subjects. For instance, among ever smokers, only 19 had started to smoke later than the age of 20 years, and of those, only 2 began later than 30 years of age. We note too that our study is one of the few to adjust age at initiation for other measures of smoking. In particular, we adjusted for pack-years as well as time since smoking cessation. A recent analysis reported that age at smoking initiation ceased to contribute independently to lung cancer risk when adjusted for cigarette-years (cigarettes/day \times the number of years smoked) and time since smoking cessation (46).

No clear association was observed for quitting smoking (Table 3), and in particular, no reduction of risk of testicular cancer was demonstrated with increased time since quitting. Former smokers maintained increased risks relative to nonsmokers (Table 2). We found no statistically significant differences between former and current smokers at a given level of pack-years or years smoked; Gallagher *et al.* (5) noted a suggestive increased risk among ex-smokers compared with current smokers (OR = 1.2, 95% CI: 0.9–1.6). That the risk of cancer did not decline with time suggests that cigarette smoke exposure may act as an early stage carcinogen in testicular cancer, *i.e.*, that it likely serves an earlier rather than later role in a presumed multistep carcinogenic process. This suggestion would have greater weight were age at initiation associated too with subsequent risk. Differential misclassification may have resulted from cases who may have quit upon diagnosis because the time between diagnosis and questionnaire return, however,

was an average of 234 days, with 90% of subjects < 378 days and none > 2 years; our specified minimum quitting period of 2 years should have accounted for any such misclassification. Furthermore, smokers who had quit upon or shortly before diagnosis would not have been included in the categories of extended time since smoking cessation, *e.g.*, >7 years, which also did not display any protective benefit of quitting. It is true that the category with the largest OR was that of those who had most recently quit, with successively smaller ORs; the wide CIs, however, mitigate any substantive conclusions about misclassification. It is possible too that any effect of quitting may be observed only after an extended period of time such as the 15 years (47) or 25 years (48) necessary for even a modest reduction to be experienced with renal cell cancer; because testicular cancer is largely a disease of younger males, such an opportunity for an extended quitting time may be relevant to relatively few cases.

Our study is the first to have examined thoroughly the relation between cigarette smoke and testicular cancer. Our study results offer evidence for a relationship between smoking and risk of testicular cancer, such that among those who have ever smoked, the observed effect magnitude and precision at moderate to high levels of smoking support the claim of a moderate and adverse association with testicular cancer risk. It is possible that carcinogenic constituents of smoke and/or influences on sex hormones mediate an increased risk among smokers. We noted no association with age of initiation and no reduction of risk with smoking cessation. Our findings can be used to strengthen smoking prevention programs among young males because the threat of an increased risk of a sexual cancer in one's youth is likely to resonate strongly.

Acknowledgments

We thank the Laboratory Centre for Disease Control of Health Canada, which provided financial support, made possible through the Action Plan on Health and the Environment. We also thank Professor Muni Srivastava for his helpful advice.

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