SMOKING AS RISK FACTOR FOR CARPAL TUNNEL SYNDROME: A BIRTH COHORT STUDY

Hulkkonen Sina[1], MD, Auvinen Juha[2], PhD, Miettunen Jouko[2], Prof, Karppinen Jaro[3], Prof, Ryhänen Jorma[1], PhD

1. Department of Hand Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

2. Center for Life Course Health Research, University of Oulu, Oulu, Finland

3. Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland

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CORRESPONDENCE:

Hulkkonen Sina, Department of Hand Surgery, Helsinki University Hospital and University of Helsinki, Finland, P.O. Box 266, FI-00029 HUS, Finland

Tel: +35841-4365587

Email: sina.hulkkonen@gmail.com

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ABSTRACT

Introduction: Our aim was to determine whether maternal smoking and offspring's own smoking affect the offspring's risk for carpal tunnel syndrome (CTS).

Methods: The study sample consisted of the Northern Finland Birth Cohort 1966 (N=8,703). Information on maternal smoking was collected from the participants' mothers. At 31 years, information on smoking, BMI, socio-economic status, and long-term illnesses were collected, combined with data of CTS diagnoses from the Care Register for Health Care (1997–2016).

Results: Maternal smoking was not associated with increased risk of CTS in offspring. Before the age of 31 years, smoking ≤10 pack years (hazard ratio [HR]=1.54, 95% confidence interval [CI]=1.11–2.15) and >10 pack years (HR=1.90, 95% CI=1.20–3.01) among women, and >10 pack years (HR=1.89, 95% CI=1.14–3.12) among men, was associated with CTS compared to non-smokers.

Discussion: In this birth cohort, offspring's own smoking was associated with CTS, however maternal smoking was not.

KEYWORDS: epidemiology; birth cohort; carpal tunnel syndrome; upper extremity; tobacco

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy[1–3]. CTS is common in the working population, causing sick leave and resulting in higher health care costs[4,5]. Smoking has been recognized as a risk factor for CTS in cross-sectional studies[6–10], but not in cohort studies[11–15]. In some studies, smoking did not increase[16,17], or even reduced, the risk for CTS[18,19].

Maternal smoking is associated with increased hospitalization of offspring, as well as neurobehavioral and musculoskeletal problems in adolescence[20,21]. Cigarette smoke is recognized as a neuroteratogen in animal models[22]. We found no previous studies about smoking during pregnancy and entrapment neuropathies in humans.

The hypotheses of this study were that both maternal smoking and offspring's own smoking are associated with increased risk for CTS in offspring; and that the risk of CTS increases according the magnitude of exposure to smoking.

METHODS

Study population

The study population consisted of the Northern Finland Birth Cohort 1966 (NFBC1966). The cohort participants have been studied at several time points throughout their lives. We used prenatal

data collected from the cohort participants' mothers during pregnancy, and data collected in the cohort's 31-year assessment in 1997 (the baseline). In the follow-up between 1997 and 2016, we studied the incidence of CTS in the NFBC1966 in relation to these data.

The NFBC1966 originally included 12,231 children with an expected birth date in 1966 in the two northernmost provinces of Finland, Oulu, and Lapland. The prenatal data was collected from mothers of 12,065 children. In 1997, altogether 8,719 cohort participants were alive, living in Finland and gave their informed consent to participate in the study at the 31-year assessment. Of those, 16 participants were diagnosed with carpal tunnel syndrome before the age of 31 and were excluded, leaving a total of 8,703 participants that were included in the study (Supplementary material Figure 1).

In handling the data, each participant's personal identification was replaced with a study identification code. The study followed the principles of the Declaration of Helsinki. Both the participants and their mothers signed a written informed consent to voluntarily participate in the NFBC1966. The study was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District.

Study outcome

The data on diagnosed carpal tunnel syndrome, from 1981 onwards, was obtained from the Finnish Care Register for Health Care, a national register covering both public and private hospitals in

Finland. The data identifies over 95% of discharges and has a positive predictive value of 75–99% for common diagnoses[23]. It contains information about patients' demographic features, dates of inpatient and outpatient hospital appointments, admission and discharge, primary and subsidiary diagnoses, and surgical procedures. The diagnoses are coded according to the International Classification of Diagnoses (ICD). The diagnosis of CTS was coded 357.2 according to the eighth revision from 1981 to 1986, 354.0 according to the ninth revision from 1987 to 1995, and G56.0 according to the tenth revision from 1996 to 2016. The diagnoses were obtained from hospital data, which includes both inpatient- and outpatient-based services in specialist care.

Prenatal data

Prenatal data was collected from cohort participants' mothers at 24 to 28 weeks of gestation using a questionnaire. If this did not occurre, the questionnaire was administered later in the pregnancy or after delivery (10.1% of the mothers). The questionnaire included several questions about maternal smoking: "Have you smoked during the last 12 months before pregnancy?"; "How long have you smoked? (years)"; "How many cigarettes? (daily)"; and "Did you change your smoking habits during pregnancy?" If the mother reported a change in her smoking habits, the type of change, month of pregnancy in which the change occurred, and number of cigarettes per day after the change, was recorded. Two groups were formed: no smoking or quit smoking in the first three months of pregnancy (no maternal smoking); and smoking throughout the pregnancy or gave up later in the pregnancy (maternal smoking).

Study population at baseline (31 years)

Data at the 31-year assessment were collected via postal questionnaire and at clinical examination[24]. The postal questionnaire asked: “Have you ever smoked in your life?” If answered “yes” the smoking habits were further clarified with questions: “Have you ever smoked regularly in your life?”; “At what age did you start smoking?” and “At what age did you quit smoking?”. The number of cigarettes, cigarillos, pipefuls, and cigars was recorded. Three variables describing smoking before the age of 31 years were collected: history of regular smoking (yes/no), pack years, and pack years based on three categories (non-smokers, smokers with history of ≤10 pack years, and smokers with >10 pack years). Pack years were calculated by multiplying regular smoking years with the amount of tobacco consumed. One pack was assumed to contain 20 cigarettes, cigarillos, or pipes, and one cigar equated to four cigarettes[25].

Socioeconomic status was defined by occupation and activity in working life according to Socio-economic Groups Classification of Statistics Finland 1989: farmers, entrepreneurs, upper and lower employees, manual workers, students, pensioners, unemployed, and unknown[26]. The variable was divided into three categories describing the physical workload and activity in working life: upper and lower employees (hereby referred as clerical workers) and entrepreneurs as reference; farmers and manual workers; and students, pensioners and unemployed. Body mass index (BMI) was calculated from height and weight measurements in clinical examination or, if missing, height and weight information of the postal questionnaire. This was divided into two categories: BMI under 25 (underweight/normal) and BMI 25 or higher (overweight/obese).

Statistical analysis

All the analyses were stratified by gender. The correlations between background factors, smoking, and CTS were studied using Fisher's exact and Chi-square tests, T-tests for normally distributed and Mann-Whitney U-test for non-normally distributed continuous variables. To investigate different background factors and their association with CTS, multiple Cox's regression proportional hazard models were used in univariate and multivariate models; An association was considered significant if hazard ratios (HR) with 95% confidence intervals (CI) excluded 1, and with $P<0.05$. Based on the literature for smoking and CTS, the background factors were chosen for further analyses[27–29]. Kaplan-Meier plots were added to visualize the outcome incidence in different groups.

The population attribute risk percent (PAR%) for regular smoking was calculated by adjusting with the same background factors as multivariate Cox's proportional regression analyses, with a target value of no smoking. The statistical analysis was performed using R version 3.4.2.

RESULTS

The study population is described in Table 1. During the follow-up between 1997 and 2016 (mean=18.24, SD=4.26 years), a total of 308 (3.5%) patients with carpal tunnel syndrome were

diagnosed. The incidence of CTS was 2.60 per 1000 person years in women and 1.23 per 1000 person years in men.

Maternal smoking

Maternal smoking correlated with offspring's own smoking in both genders, with socioeconomic status among men, and with diabetes among women. We found no correlation between maternal smoking and offspring's CTS or BMI for either gender (Supplementary material Table 1).

In both univariate and multivariate Cox's proportional hazards regression models tested, maternal smoking was not associated with elevated risk for CTS in the offspring (Supplementary material Table 2). Supplementary material Figure 2 illustrates the study participants' outcomes (new cases of CTS) in follow-up, stratified by maternal smoking. Adjusted for the same background factors as multivariate Cox's proportional hazards regression models, PAR% of regular smoking was 5.4 for men and 1.9 for women.

Offspring's own smoking

Offspring's own smoking correlated with CTS, BMI, and socioeconomic status among women. Among men, smoking correlated with socioeconomic status and BMI, but not with CTS (Table 2).

In the univariate Cox's proportional hazards models tested, smoking and overweight/obesity were associated with higher risk for CTS among men and women, diabetes associated with higher risk only among women. Students, retired, and unemployed men, and both male and female farmers and manual workers were at increased risk for CTS compared to clerical workers and entrepreneurs. In multivariate models adjusted for smoking, BMI, socio-economic status, and diabetes, the history of regular smoking ten or less pack years by the age of 31 was associated with 1.5-fold increased risk for CTS later in life among women, as smoking over ten or more pack years nearly doubled the risk among men and women compared to non-smokers. In both genders, farmers and manual workers had a higher risk for CTS compared to clerical workers and entrepreneurs. Overweight/obesity was associated with a higher risk for CTS in both genders as well (Table 3). PAR% of regular smoking was 20.8 for women and 13.9 for men, compared to non-smokers adjusted for the same background factors as multivariate Cox's proportional hazards models. Figure 1 illustrates the outcomes of study participants in follow-up, stratified by smoking.

DISCUSSION

We found that maternal smoking is not associated with elevated risk for CTS in offspring, but offspring's own smoking is. Among both men and women, regular smoking of over ten pack years before the age of 31 was associated with nearly doubled risk for CTS later in life compared to non-smokers, when adjusted for BMI and socioeconomic status. PAR% for smoking was higher among women compared to men when adjusted for BMI and socioeconomic status. This finding

demonstrates that smoking is associated with an elevated risk for carpal tunnel syndrome, especially among women.

The association between maternal smoking and peripheral neuropathies in offspring is unclear. There are only a limited number of longitudinal studies conducted in the general population that investigate whether smoking is associated with elevated risk for CTS. Nonetheless, compared to previous longitudinal studies published about CTS[11,12,15], our sample size is larger. The NFBC1966 represents the Finnish general population very well, as it covers nearly all persons born in Northern Finland in 1966. The participants are the same age, and come from different backgrounds and all socio-economic classes. The mean follow-up time of this study was long. We assessed not only the history of smoking but also the amount of smoking by calculating pack years.

Despite the large sample size of the cohort, a limitation of this study is the relatively small number of cases, as only 308 developed CTS out of 8,703 participants during the 19-year follow-up (1997–2016). This might be due the data we used and the relatively young age of participants. In Finland, the public healthcare system includes both health centers and hospitals. We only used data from hospitals, because suspicion of CTS is usually coded under the same ICD code in health centers and thus health-center data would not be as reliable as hospital data. Thus, some patients with only mild CTS symptoms or patients who were not willing to consider an operation or visit a hospital polyclinic would go unrecognized. Other limitations include the fact that the diagnoses were not verified from patient records of the participants. As the incidence of CTS has two peaks, at 50 to 59 years and at 70 to 79 years of age, ending the follow-up when the cohort population had just turned

50 years might explain the relatively small number of cases in our study sample[2]. Also, only 14.5% of the mothers continued smoking after the second month of pregnancy, so the number of cases with maternal smoking in our study was small (19 men and 38 women), which might limit the statistical power.

Previous studies suggest that maternal smoking might cause damage to the developing nervous system and could lead to various problems in adolescence[20,21,30]. Maternal smoking and offspring's own smoking are correlated, meaning that children of smoking mothers are more prone themselves to smoke in the future. The PAR% for maternal smoking was much lower compared to those for offspring's own smoking, implying that offspring's smoking played a greater role in increasing the risk of CTS than maternal smoking.

The etiology of the relationship between nerve compression disorders, personal factors, and environmental factors is unclear. Personal factors, such as diabetes mellitus, hypothyroidism, alcohol use, and smoking, have been assumed to be part of the etiology[7,19]. Overweight/obesity is an independent risk factor for CTS among both men and women[31]. In this study we mainly focused on smoking as a risk factor for CTS. It has been hypothesized that smoking could impair the vascular supply of the median nerve, which could lead to nerve degeneration and fibrosis leading to CTS[9,32,33]. In our cohort, half of men and a third of women had smoked regularly. Heavy smoking in adolescence (over 10 pack years before the age of 31 years) was associated with nearly double the risk for CTS in both men and women later in life. Although all other covariates behaved similarly among both men and women, smoking ten or less pack years in adolescence was

surprisingly associated with elevated risk for CTS only among women. Compared to previous longitudinal studies, we found a stronger correlation with smoking and CTS[11–14]. Work-related factors, such as significant exposure to vibration and some specific occupations, may be associated with a high prevalence of CTS, but the problem is still debated[6,8,17]. In our cohort, farmers and manual workers were at increased risk for CTS compared to clerical workers and entrepreneurs, as expected based on previously published literature[28,29,34]. Among women, overweight/obesity was associated with CTS. These results are in line with previous studies[28,29,31]. However, there might be one or more confounding factors that are not included in our analysis, and that could explain the correlation between CTS and the background factors tested. For example, genetic factors that might play a role in the etiology of CTS[35] were not addressed in the current study population.

To conclude, we found that offspring's own smoking is associated with an elevated risk for CTS in offspring, but maternal smoking is not. Further studies are needed to study these topics in a normal population of all ages with longer follow-up. As previous studies have suggested that smoking might interfere with the normal development of the nervous system[20,30], further studies about maternal smoking affecting offspring's peripheral nervous system are needed.

ABBREVIATIONS

BMI, body mass index

CI, confidence interval

CTS, carpal tunnel syndrome

HR, hazard ratio

NFBC1966, the Northern Finland Birth Cohort 1966

ICD, the International Classification of Diagnoses

PAR, population attributable risk

SD, standard deviation

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FIGURE CAPTIONS

Figure 1 Kaplan-Meier curves for CTS in follow-up, stratified by smoking status.

1A Men

1B Women

Table 1. Basic demographic features of the study population stratified by gender.

	Men, n=4,156	Women, n=4,547	P-value
Carpal tunnel syndrome, n (%)	94 (2.3)	214 (4.7)	<0.001
Maternal smoking after second month of pregnancy, n (%)			NA
Yes	585 (14.5)	628 (14.4)	
No	3,405 (85.3)	3,740 (85.6)	
At the age of 31 years			
History of regular smoking, pack years			<0.001
No, n (%)	1,756 (49.3)	2,452 (63.0)	
Ten or less, n (%)	960 (27.0)	1,118 (28.7)	
Over ten, n (%)	846 (23.7)	323 (8.3)	
Mean (sd)	5.30 (7.37)	2.41 (4.55)	
Body mass index			<0.001
Normal, n (%)	2,053 (51.0)	3,060 (70.1)	
Overweight/Obese, n(%)	1,969 (49.0)	1,305 (29.9)	
Mean (sd)	25.27 (3.60)	23.92 (4.47)	
Socio-economic status, n (%)			<0.001
Clerical workers, entrepreneurs	1,801 (45.5)	2,796 (66.0)	
Students, retired, unemployed	526 (13.3)	675 (15.9)	
Manual workers, farmers	1626 (41.1)	764 (18.0)	
Diabetes, n (%)	40 (1.0)	72 (1.6)	0.014
Thyroid disease, n (%)	25 (0.6)	137 (3.1)	<0.001
Rheumatoid arthritis, n (%)	27 (0.7)	62 (1.4)	0.01

	Men, n=4,156	Women, n=4,547

Table 2. Cross-tabulation between smoking and other background factors stratified by gender.

	History of regular smoking		P-value	History of regular smoking		P-value
	Yes	No		Yes	No	
Carpal tunnel syndrome	57 (2.5)	33 (1.9)	0.194	115 (5.9)	87 (3.5)	<0.001
At the age of 31						
History of regular smoking, pack years			<0.001			<0.001
No, n (%)	0 (0.0)	1,756 (100.0)		0 (0.0)	2,452 (100.0)	
Ten or less, n (%)	960 (53.2)	0 (0.0)		1,118 (77.6)	0 (0.0)	
Over ten, n (%)	846 (46.8)	0 (0.0)		323 (22.4)	0 (0.0)	
Mean (sd)	10.46 (7.29)	0.00 (0.00)	<0.001	6.50 (5.42)	0.00 (0.00)	<0.001
Body mass index			0.045		23.75 (4.28)	0.028
Normal, n (%)	1,106 (49.8)	924 (53.0)		1,304 (68.3)		
Overweight/Obese, n(%)	1,117 (50.2)	819 (47.0)		604 (31.7)		
Mean (sd)	25.37 (3.65)	25.15 (3.54)	0.058	24.12 (4.68)		0.007
Socio-economic status, n (%)			<0.001			<0.001
Clerical workers, entrepreneurs	829 (37.9)	954 (55.5)		1,092 (58.4)	1,681 (72.3)	
Students, retired, unemployed	323 (14.7)	198 (11.5)		353 (18.9)	315 (13.5)	
Manual workers, farmers	1,039 (47.4)	567 (33.0)		424 (22.7)	329 (14.2)	
Diabetes, n (%)	22 (1.0)	17 (1.0)	1.000	31 (1.6)	39 (1.6)	1.000
Thyroid disease, n (%)	11 (0.5)	14 (0.8)	0.313	70 (3.6)	66 (2.7)	0.102
Rheumatoid arthritis, n (%)	14 (0.6)	12 (0.7)	0.982	31 (1.6)	29 (1.2)	0.299

Table 3. Cox's proportional hazards regression models stratified by gender.

	Men, n=4,156		Women, n=4,547	
	HR (95% CI)		HR (95% CI)	
Model	Univariate	Multivariate	Univariate	Multivariate
History of regular smoking, pack years				
No	1	1	1	1
Ten or less	0.99 (0.56–1.77)	0.94 (0.52–1.71)	1.59 (1.15–2.20)*	1.54 (1.11–2.15)*
Over ten	2.05 (1.26–3.34)*	1.89 (1.14–3.12)*	2.30 (1.46–3.62)*	1.90 (1.20–3.01)*
Body mass index				
Normal/Underweight	1	1	1	1
Overweight/Obese	1.83 (1.20–2.80)*	1.59 (1.01–2.49)*	2.07 (1.57–2.72)*	1.91 (1.41–2.59)*
Socioeconomic status, n (%)				
Clerical workers, entrepreneurs	1	1	1	1
Students, retired, unemployed	2.25 (1.15–4.40)*	1.93 (0.96–3.88)	1.33 (0.89–2.00)	1.32 (0.86–2.02)
Manual workers, farmers	2.67 (1.62–4.39)*	2.18 (1.29–3.69)*	2.42 (1.77–3.30)*	2.24 (1.58–3.17)*
Diabetes				
No	1	1	1	1
Yes	1.16 (0.16–8.34)	1.42 (0.20–10.20)	2.57 (1.27–5.21)*	2.11 (0.86–5.17)
Thyroid disease	NA			
No			1	
Yes			1.49 (0.76–2.90)	
Rheumatoid arthritis				
No	1		1	
Yes	1.77 (0.25–12.72)		1.14 (0.36–3.57)	

*p<0.05