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The association between cigarette smoking and multiple sclerosis

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ABSTRACT

Genetic factors partially explain the susceptibility of multiple sclerosis (MS) and might even relate to the clinical course. Still, many epidemiological studies point at an important role for environmental factors in MS. Smoking is one of the major candidates. In this review we provide an overview of the epidemiological studies on cigarette smoking and the association on MS risk and MS clinical course. In addition, we discuss the possible biological pathways that may influence neurological damage in MS. Moreover, the relation of smoking with other environmental MS risk factors will be addressed.

1. Introduction

Multiple sclerosis (MS) is regarded as a disease with a multifactorial aetiology, comprising genetic as well as environmental influence. Migration studies, geographical gradients and high rates of discordance in identical twins point to the influence of environmental factors interacting with genetics in determining disease susceptibility [1]. The landmark work of Kurtzke [2] showed that the MS risk declined twofold with migration from high- to low-risk areas which indicate that genetic factors can account for only a small proportion of geographical MS variety. This was also supported by others [3], suggesting a role for a range of physical, chemical, biological and social environmental factors. Moreover, the evidence on the rising worldwide prevalence and increasing female to male ratio focuses the interest on environmental factors [4].

The environmental risk factors implicated include sun exposure, vitamin D status, Epstein–Barr virus (EBV) infections and smoking. These factors combined can interact at different time points prior to and following the clinical onset of MS [5]. Cigarette smoking is emerging as one of the most postulated environmental risk factors linked to onset and clinical course of MS in genetically susceptible individuals [6,7]. The history of the suggested association between MS and smoking goes back to the 1960s when few studies were performed, although these studies did not reach significance and analysed a large number of variables simultaneously [8,9].

In this review we aim to give an overview of the studies conducted on the association between smoking and MS susceptibility, and clinical course. In addition, we discuss the possible pathogenic role of smoking in MS and the related underlying mechanisms. Finally, we provide some arguments supporting, but also some challenging this association.

2. Cigarette smoking and risk of MS

Several retrospective and prospective studies have investigated the association between smoking and MS susceptibility. Table 1 gives a chronological summary of the key studies. One of the earliest papers to include smoking habit was an exploratory case–control study from Israel in 1965 [8], where 241 MS patients were questioned about ever smoking prior to disease onset. The control group included 964 subjects individually matched to patients by age, sex and region of birth. They found significantly more previous smokers in the patient group (44% vs. 36%, $p = 0.02$). However, they did not correct for multiple comparisons.

It was not until the 1990s that two longitudinal studies among women in the United Kingdom [10,11] showed that women who regularly smoked were found to have a higher risk of MS, although these findings were not significant. In the Oxford Family Planning Association Study, the incidence of MS in women who smoked ≥15 cigarettes per day was 1.8 (95% CI 0.8–3.6) times higher than in women who never smoked [10]. The Royal College of General Practitioners' Oral Contraception Study demonstrated comparable findings with the incidence of MS in women who smoked ≥15 cigarettes per day 1.4 (95% CI 0.9–2.2) times higher than never-smokers [11]. It should be noticed that both studies included only females and small number of incident cases of MS (63 and 114 respectively). Furthermore, assessing smoking history was a secondary question since both studies were conducted to investigate the possible relation of oral contraceptives and MS risk.

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Table 1
Chronological summary of fourteen main studies examining cigarette smoking and MS onset.

First author Publication year	Number of cases	Number of controls[a]	Female/male ratio	Quantity smoked (Number of cases)[b]	OR/ RR (95% CI)	Adjustments and/or matching	Study type and comment (Country)
Antonovsky et al. [8]	241	964	0.8	Ever-smoker (106)	OR 1.4 (1.1–1.9)	Age, sex, region of birth	Case–control study. (Israel)
Villard-Mackintosh and Vessey [10]	63	17,032	All females	Ex-smoker (9) Current smoker (26) 1–14/day (14) ≥15/day (12)	RR 1.5 (0.6–3.3) RR 1.6 (0.8–3.1) RR 1.8 (0.8–3.6)	Age, parity, clinic, date of admission to study	Prospective cohort study. (UK)
Thorogood and Hannaford [11]	114	46,000	All females	Ever-smoker (58) 1–14/day (33) ≥15/day (25)	 RR 1.2 (0.8–1.8) RR 1.4 (0.9–2.2)	Age, parity, social class	Prospective cohort study. Incident cases. All smokers started before disease onset. (UK)
Ghadirian et al. [15]	200	202	2.2	Ever-smoker (138) 0–<10/day (15) 10–20/day (34) 20–40/day (71) ≥/40/day (16)	OR 1.6 (1.0–2.4) OR 0.7 (0.3–1.5) OR 1.4 (0.8–2.4) OR 1.9 (1.2–3.2) OR 5.5 (1.7–17.8)	Age, sex, education	Incident case–control. Smoking in year prior to diagnosis. (Canada)
Hernan et al. [12]	315	237,264	All females	Ex-smoker (79) Current smoker (96) Ever-smokers (175) 1–9 pack years (43) 10–24 pack years (75) >25 pack years (57)	RR 1.2 (0.9–1.6) RR 1.6 (1.2–2.1) RR 1.1 (0.8–1.6) RR 1.5 (1.2–2.1) RR 1.7 (1.2–2.4)	Age, latitude, ancestry.	Prospective study in NHS and NHS II[c] cohorts. Smoking 4 years prior to MS diagnosis. (USA)
Riise et al. [21]	86	22,312	NR	Ever-smoker (65) Female (NR) Male (NR)	RR 1.8 (1.1–2.9) RR 1.6 (ns) RR 2.8 (ns)	Age, sex	Population based cross-sectional study. (Norway)
Zorzon et al. [16]	140	131	1.8	Ever-smoker (79) Current smoker (58)	OR 1.5 (0.9–2.4) OR 1.9 (1.1–3.2)	Age, sex	Case–control study. (Italy)
Hernan et al. [13]	201	1913	2.4	Ex-smoker (NR) Current smoker (NR) Ever-smoker (92)	OR 1.0 (0.6–1.8) OR 1.4 (1.0–1.9) OR 1.3 (1.0–1.7)	Age, sex, family practise, date of joining practise and availability of smoking information	Prospective, nested case–control study. (USA)

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