Epidemiology of Multiple Sclerosis: From Risk Factors to Prevention

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ABSTRACT

Although genetic susceptibility explains the clustering of multiple sclerosis (MS) within families and the sharp decline in risk with increasing genetic distance, it cannot fully explain the geographical variations in MS frequency and the changes in risk that occur with migration, which support the action of strong environmental factors. Among these, vitamin D status, infection with the Epstein-Barr virus, and cigarette smoking are emerging as the most consistent predictors of MS risk. In this article, we review the epidemiological data, critically discuss the evidence for causality of these associations, and briefly discuss the possibility of interventions to reduce MS risk.

KEYWORDS: Multiple sclerosis, epidemiology, vitamin D, infection, environment

In spite of advances in medicine and related sciences, the largest contributions to health and increased life expectancy have historically come from primary prevention. Is the primary prevention of multiple sclerosis (MS) an attainable goal? We briefly review here what is known about risk factors for MS and suggest that we may now have sufficient evidence to prevent at least some cases of MS and that growing understanding of the environmental risk factors for MS may soon lead to more effective prevention strategies.

Although clinically and pathologically MS is a complex and heterogeneous disease,1 these distinctions are difficult to establish in epidemiological studies and have thus been mostly ignored, except for occasional attempts to differentiate primary progressive MS from the more common relapsing-remitting MS. In this article, therefore, we refer to MS as a single entity, acknowledging the possibility that there are subtypes of MS that may differ in their risk factors.

EVIDENCE OF ENVIRONMENTAL RISK FACTORS OF MULTIPLE SCLEROSIS

MS is a relatively common disease in most of Europe, the United States, Canada, New Zealand and southern Australia, but rare in Asia, the tropics, and the subtropics. Within regions of temperate climate, MS incidence and prevalence increase with latitude, both north and south of the equator.2,3 The lifetime risk of developing MS in high-risk populations is ~1 in 200 for women.4,5 In virtually all populations, women are affected more commonly than men, with the female-to-male ratio varying between 1.5 and 2.5, with a trend toward higher values in the most recent studies.6 The age at onset follows a relatively constant pattern across different regions: incidence is low in childhood; rapidly increases after adolescence, reaching a peak between ages 25 and 35 years (~2 years earlier in women than men); and then slowly declines.

The strongest known risk factor for MS is a positive family history. Risk of MS is ~30 times higher

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among siblings of affected individuals than in the general population. The results of detailed studies of familial aggregation, including the investigation of risk among half-siblings and adopted children, provide convincing evidence that the aggregation of MS within families is largely explained by shared genes rather than a shared environment. Consequently, large international consortia have been established to identify the genetic determinants of MS; although only the HLA-DRB1 locus has so far been firmly linked to MS risk, other important loci are likely to be discovered through systematic screening of the whole genome.

In contrast, support for environmental risk factors rests primarily on the geographical distribution of MS and changes in risk among migrants. Important examples include studies of people who migrated from different countries to Israel, from the United Kingdom to South Africa and Australia, and from U.S. locations to other U.S. locations (Fig. 1). The U.S. migrant studies are particularly compelling because they are based on a very large number of MS cases (>5,000) and involve a population with relatively complete and uniform rates of ascertainment (U.S. veterans). In all these instances, the incidence of MS in migrants tends to be intermediate between that of their birthplace and that of their final residence, and close to the latter when migration occurs in childhood. Although genetic predisposition most likely contributes to geographical variations in MS incidence, it cannot explain the differences in risk among people of common ancestry who migrate to areas of high or low MS prevalence. Further, the recent marked decline in the latitude gradient of MS incidence in the United States provides additional evidence for an environmental cause.

**Sunlight Exposure and Vitamin D**

Many geographical and socioeconomic factors display a latitude gradient that correlates with the prevalence of MS; therefore, inferring from the migrant data which of these factors may be etiologically relevant has proven difficult. An early study among U.S. veterans attempted to dissect the role of multiple factors, including air pollution, concentration of minerals in ground water, measures of annual solar radiation, mean temperature, annual rainfall, humidity, and altitude. Although each factor when examined alone correlated with MS incidence, none of these factors remained significantly related to MS risk after adjustment for latitude. This result suggests that latitude itself, or a closely related factor, may influence MS risk.

One of the strongest correlates of latitude is the duration and intensity of sunlight. Strong correlations between sunlight and MS prevalence were noted in early ecological studies, and a link between sunlight radiation and reduced MS risk was further supported by the finding of an inverse correlation in Switzerland between MS prevalence and altitude, which is also a marker of sunlight intensity. Largely because of these correlations, it was proposed more than 30 years ago that the higher incidence of MS at higher latitudes could be due to vitamin D deficiency. Exposure to sunlight is for most people the major source of vitamin D. Ultraviolet B (UVB) radiation (290 to 320 nm) converts...
cutaneous 7-dehydrocholesterol to previtamin D₃, which spontaneously isomerizes to vitamin D₃. Vitamin D₃ then undergoes a series of hydroxylations, first to 25-hydroxyvitamin D₃ (25(OH)D₃), the main circulating form of the vitamin, and then to 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃), the biologically active hormone.²⁷ However, at latitudes ≥ 42° (e.g., Boston, MA) in winter most UVB radiation is absorbed by the atmosphere; even prolonged sun exposure is insufficient to generate vitamin D,²⁸ and vitamin D levels drop.²⁹,³⁰ Although use of supplements or high consumption of fatty fish, a good source of vitamin D, or vitamin D–fortified foods (mostly milk in the United States) may attenuate this decline, average levels of vitamin D display a strong latitude gradient. The hypothesis that vitamin D deficiency could increase MS risk could provide a reasonable explanation for the latitude gradient and change in risk among migrants. This hypothesis is also supported by the finding in Norway that MS prevalence is lower in coastal villages with higher fish consumption than in inland agricultural communities.³¹,³²

People living in the same area, however, share many characteristics whose possible contributions to MS risk cannot be separated in ecological studies. To overcome this limitation, it is critical to compare the risk of MS among individuals living in a similar environment, but exposed to different levels of vitamin D. Numerous studies have attempted these comparisons, using measures of sun exposure, vitamin D intake, or direct measurement of vitamin D levels in serum, as described in the following sections.

### Studies Based on Death Certificates or Record Linkage

In an exploratory investigation based on death certificates, MS mortality in areas of high and low sunlight was related to the individual's usual occupation, classified by an industrial hygienist as indoor, mixed, or outdoor.³³ After adjusting for age, sex, and socioeconomic status, both outdoor work (odds ratio = 0.53) and residence in high sunlight areas (odds ratio = 0.74) were associated with lower MS mortality, consistent with a protective effect of sunlight exposure. Most importantly, working outdoors was associated with a significantly lower MS mortality in areas of high, but not low, sunlight.³³ Major limitations of this study included reliance on death certificates, which are an inaccurate source for both cause of death and occupation, and the possible effects of “reverse causation,” that is, individuals with MS could preferentially choose an indoor rather than an outdoor occupation.

In a U.K. study using a record-linkage analysis, the observed rates of skin cancer among individuals with MS was compared with that expected according to sex- and age-adjusted population rates in the same districts.³⁴ Because the association between sun exposure and risk of skin cancer is well-established, the hypothesis was that individuals with MS would have a lower risk of skin cancer. In fact, skin cancer rates among individuals with MS was found to be ∼50% lower than the expected (p = 0.03). This result provides evidence of reduced sun exposure among individuals with MS, but it remains unclear whether this reduced exposure is the cause or the consequence of MS. The latter possibility seems quite plausible because individuals with MS may spend less time outdoors and may reduce their exposure to direct sunlight because of heat intolerance.

### Case-Control Studies

A more direct attempt to measure exposure to sunlight before the onset of MS was conducted in a few case-control studies. In these studies, individuals with MS were asked to recall the time that they spent in the sun at different ages before the onset of MS, and their answers were compared with those of unaffected individuals in the same population. Although these investigations should be less affected by the impact of MS on sun exposure than the studies based on death certificate or record linkage, bias from differential recall of MS cases and controls cannot be excluded. Also, participation rates among controls are often low, and if participation in the study is related to sun exposure (for example, if individuals spending more time indoors are more likely to be contacted and interviewed), bias may result. These limitations should be considered in interpreting the results.

A question on exposure to sunlight was included in two early case-control studies, which were designed to explore a broad range of environmental factors. In the first study, conducted in Israel, individuals with MS (n = 241) reported significantly more time spent outdoors in the summer during childhood than age- and sex-matched healthy controls, a result opposite to that predicted if sunlight exposure was protective (Fig. 2A).³⁵ In the second, including 300 MS cases in Poland, no association was found between time in the sun before MS onset and MS risk (Fig. 2B).³⁶

A more targeted attempt to address the possible role of sun exposure in determining MS risk was made in a study including 136 MS cases in Tasmania. The protocol of this study included not only a detailed assessment of sun exposure at different ages, but also measurement of actinic skin damage, an indicator of lifelong exposure to sunlight.³⁷ The correlation between actinic skin damage and self-reported exposure to sunlight in childhood provided evidence of the validity of the questionnaire.³⁸ The relative risks of MS among individuals who reported on the questionnaire an average time in the sun of 2 hours or more between the ages of 6 and 10 years were 0.47 (95% confidence interval
(CI): 0.26 to 0.84) for winter exposure and 0.50 (95% CI: 0.24 to 1.02) for summer exposure (Fig. 2C). Inverse, but weaker associations were observed with sun exposure at older ages. Stronger associations and significant trends were found using the interview-based recall of exposure ($p$ for trend $< 0.01$, for ages 6 to 15 years) or actinic damage ($p$ for trend $< 0.01$). Although differential reporting of sun exposure between cases and controls, and thus recall bias, cannot be excluded, this could not explain the inverse association with actinic damage, which was objectively measured. On the other hand, results based on actinic damage are prone to error due to reverse causation (a limitation already discussed for the occupation and record-linkage studies) because actinic damage measures cumulative exposure to sunlight, including during the years following MS onset.

Finally, an interesting study was recently conducted in northern Norway, in counties above the Arctic Circle (latitudes 66 to 71 N). At this latitude, during winter virtually all vitamin D is provided by diet; the most important sources are fatty fish and cod-liver oil, which is rich in vitamin D and commonly used as a supplement. MS cases ($n = 152$) and matched controls ($n = 402$) were asked to report both the time spent in outdoor activities at different ages and their consumption of fish and cod-liver oil supplements in childhood. Time spent outdoors in the summer was...
associated with a reduced risk of MS, most pronounced at ages 16 to 20 years (45% lower risk, \( p \) for trend = 0.001) (Fig. 2D). An inverse association was also found between frequent fish consumption and MS risk, whereas use of cod-liver oil was inversely associated with MS risk only among individuals who reported low summer outdoor activities.

**Longitudinal Studies**

The association between diet and risk of chronic diseases is difficult to investigate retrospectively because even a modest difference in recall between cases and controls can cause a large bias in relative risk estimates.\(^4^0\) Similar considerations apply to other aspects of lifestyle that cannot be objectively documented. The probability of bias is even greater in investigations of disease that have an insidious onset, because the disease itself may induce changes in lifestyle and diet before a diagnosis is made. Thus, a longitudinal study design with a long period of follow-up is important to ensure the validity of the results. Because MS is a relatively rare disease, longitudinal studies need to be very large and, not surprisingly, only a few have been conducted.

The only published longitudinal study on dietary vitamins and MS risk was conducted among participants in two large cohorts of U.S. nurses, the Nurses Health Study and the Nurses Health Study II, comprising more than 200,000 women\(^4^1\) who completed a validated semiquantitative food frequency questionnaire. To account for changes in diet over time, a dietary questionnaire was administered every 4 years during the follow-up.\(^4^2,4^3\)

Vitamin D intake, from both foods and vitamin supplements, was found to correlate with blood levels of 25(OH)D (available in a subset of 343 women)\(^4^4\) and to predict a reduced risk of hip fractures,\(^4^4\) thus providing evidence of its validity. Risk of developing MS during the follow-up declined with increasing vitamin D intake. The age-adjusted pooled relative risk (RR) comparing women with vitamin D intake of \( \geq 400 \) IU/d to those with none was 0.59 (95% CI = 0.38 to 0.91; \( p \) for trend = 0.006) (Fig. 3A). This RR did not materially change after further adjustment for risk factors for MS, including pack-years of smoking and latitude at birth.

![Figure 3](image_url)

**Figure 3** Relative risk (RR) of developing multiple sclerosis (MS) comparing (A) individuals who used 400 IU or more of supplemental vitamin D versus nonusers; and (B) individuals with high-versus-low serum levels of 25(OH) vitamin D. Bars represent the 95% confidence intervals of the RR estimates. Use of vitamin D supplements and high levels of serum 25(OH)D are both associated with a reduced risk of developing MS. (Data from: [A] Munger KL, Zhang SM, O’Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. Neurology 2004;62:60–65; [B] Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006;296:2832–2838.)
Because intake of vitamin D was largely from multivitamins, the possibility that the observed association was due to other micronutrients contained in the multivitamin could not be excluded. However, results of multivariate analyses combined with biological plausibility suggest that the results are more consistent with a protective effect of vitamin D itself.

An alternative approach to investigate the relation between vitamin D and MS risk relies on the use of biomarkers of vitamin D status. Vitamin D is hydroxylated in the liver to 25(OH)D, the immediate precursor of 1,25(OH)2D, the active hormonal form of vitamin D. Serum levels of 1,25(OH)2D are tightly regulated and are within the normal range even in individuals who are vitamin D deficient. In contrast, 25(OH)D levels are sensitive to both vitamin D intake and sun exposure, and are a marker of vitamin D availability to tissues, including the immune system. We therefore planned to examine whether serum levels of 25(OH)D measured in healthy young adults predict their risk of developing MS. Because of the low incidence of MS, such a study required the collection of blood samples from hundreds of thousands of individuals and a follow-up of several years. This was made possible by a very large collection of serum from healthy young adults, which was made available from the Department of Defense Serum Repository (DoDSR). Since 1990, the DoDSR has collected and stored more than 40 million serum samples left over from routine HIV and worldwide deployment-related blood tests. Personnel generally provide one sample at entry into the military and, on average, every 2 years thereafter while on active duty. In collaboration with the Army and Navy Physical Evaluation Boards, we were able to identify those individuals who developed MS after providing a blood sample. Because of seasonal variations in sun exposure and thus of 25(OH)D levels, a single blood sample may be insufficient to determine the long-term vitamin D status; we restricted the analyses to individuals with at least two blood samples collected before MS onset.

The study included 257 individuals with MS diagnosed between 1992 and 2004, and two controls matched by sex, age, race/ethnicity, and time of collection of the blood samples for each case. This design, referred to as a “nested case-control” study by epidemiologists, is an efficient equivalent to a fully prospective study, in which 25(OH)D levels are measured in all available blood samples. The control group provides information on the distribution of 25(OH)D levels among the millions of individuals at risk of developing MS, at a small fraction of the cost required for measuring all the samples. The validity of the study rests on the stability of 25(OH)D levels in stored serum, which was determined in a pilot study.

The results of this study support the hypothesis of a protective effect of 25(OH)D. Because of the marked effect of race on 25(OH)D levels (the darker the skin the lower the amount of vitamin D produced by the same levels of exposure to sunlight), analyses were conducted separately in white, African American, and Hispanic populations. Among white people, MS risk declined with increasing levels of 25(OH)D—risk was 62% lower among individuals in the highest quintile (25(OH)D > 99.2 nmol/L) compared with those in the lowest quintile (25(OH)D < 63.2 nmol/L) (Fig. 3B). Further, the reduction in risk of developing MS among individuals with high 25(OH)D levels was considerably stronger before the age of 20 years (16 to 19) than at ages 20 or older. In contrast, no significant association between 25(OH)D levels and MS was found in African Americans and Hispanics, but statistical power was low because of overall low levels of 25(OH)D and small sample size.

Summary

Overall, the results of epidemiological studies seem to support a protective role of vitamin D, particularly in childhood and adolescence. It is worth mentioning, however, that UV radiation from sunlight has immunosuppressive effects that could be independent from the synthesis of vitamin D and could contribute to MS prevention. These vitamin D–independent effects, however, do not explain the results of dietary studies. Further, these results should be interpreted in combination with those of experimental studies on the effects of vitamin D. Injection of 1,25(OH)2D3 can prevent experimental autoimmune encephalomyelitis (EAE), an animal model of MS, whereas vitamin D deficiency accelerates EAE onset. Protective effects of 1,25(OH)2D3 have also been observed in animal models of type 1 diabetes and other autoimmune diseases. The mechanisms underlying these effects are still under investigation, but are likely to include induction of regulatory T cells, and

Implications for Prevention

If vitamin D effectively reduces the risk of MS, supplementation in adolescents and young adults could be effectively used for prevention. Supplements providing between 1000 and 4000 IU per day of vitamin D would increase serum 25(OH)D to the levels associated with MS protection, without causing hypercalcemia or other known adverse side effects. Although the Institute of Medicine’s current recommendation for adequate intake of vitamin D is only 200 IU/d for adults younger than 50, and the typical amount in multivitamins is 400 IU, there is increasing consensus that these levels are far below those required for optimal bone health and the prevention of other vitamin D–related diseases. Because of the high prevalence of low 25(OH)D levels in the United States and other countries with high MS incidence, the potential for MS...
prevention is extremely high. There is therefore an urgent need to determine in a large randomized trial whether vitamin D supplements can in fact reduce MS risk.

HYGIENE HYPOTHESIS AND EPSTEIN-BARR VIRUS

In 1963, Poskanzer and colleagues, noting the similarity between the epidemiology of MS with that of poliomyelitis, proposed that MS, like poliomyelitis, could be the rare neurological manifestation of a common enteric infection.66 Risk of MS, as is true for poliomyelitis, would increase with increasing age at infection with the responsible microorganism, and would thus be more common in populations with high levels of hygiene, in which transmission of infection is delayed. This hypothesis was supported by early findings of increasing MS incidence with increasing sanitation in Israel,66 and with increasing socioeconomic status in the United States67 and the U.K.68 A specific microorganism causing MS, however, could not be found, and the hypothesis has evolved into a broader “hygiene hypothesis” according to which multiple infectious exposures in early childhood would reduce the risk of MS by modulating the immune response toward helper T cells (Th)2 and regulatory T cells and attenuating the proinflammatory Th1 cellular immunity.69,70 Common intestinal helminths, for example, induce a predominantly Th2 reaction.71 Interestingly, in a recent study, infection with intestinal helminths was found to have a striking beneficial effect in individuals with MS.71 The hygiene hypothesis could explain in part the geography of MS. In the tropical and subtropical areas where MS frequency is low, most people live in conditions that favor the transmission of multiple infectious agents. Infections with common viruses tend to occur in early childhood, and gastrointestinal infections with bacteria and parasites are common. In contrast, in temperate zones of high MS risk, infection with common viruses is often delayed to late childhood or adolescence, and intestinal parasites are rare.

An example of variations in age at infection in different populations is provided by the Epstein-Barr virus (EBV). In developing countries, almost all children are infected in the first few years of life, and typically prevalence of seropositivity is higher than 90% at the age of 4 years. In contrast, in most developed countries, not only do many children escape EBV infection until adolescence, but prevalence of seropositivity to EBV displays a latitude gradient parallel to that of MS. For example, in the United States the prevalence of EBV seropositivity among young adults ranged from more than 80% in the southeast to just above 50% in the northwest.74 Unlike intestinal parasites, EBV is not transmitted by fecal contamination, but by saliva. Thus, the age at infection reflects, in part, cultural differences (such as sharing of food and food utensils), and a young age at infection with EBV is not by itself a marker of a low level of sanitation. Early age at EBV infection is observed not only in the tropics, but also at all latitudes in Asia, including highly industrialized nations such as Japan75 and among Eskimos in Greenland. It is interesting that the same populations also have a low risk for MS.76 Notably, age at EBV infection, like MS, also positively correlates with higher socioeconomic status.74 Because of the correlation between late age at infection with EBV and MS, the epidemiology of MS is remarkably similar to that of infectious mononucleosis,77 which is a common occurrence of primary EBV infection during adolescence or later in life.

The similarities between the epidemiology of MS and that of mononucleosis are striking, and lead to the critical question of whether mononucleosis is simply a marker of a high level of hygiene during childhood or whether EBV plays a more direct role in the etiology of MS. The answer to this question rests on the observation of a paradox. Young adults who are EBV negative are clearly a subset of the “high-hygiene” set, which, according to the hygiene hypothesis, has a high MS risk. Contrary to this prediction, not only do these individuals not have a high risk of MS, but, as long as they remain EBV negative, their risk is about 10 times lower than that of EBV-infected individuals of the same age (Fig. 4).78,79 The paradox could be explained if these individuals, which comprise only a small percent of the population, carried a rare genetic mutation that confers resistance to both EBV infection and MS. This interpretation, however, has been virtually ruled out by the fact that a similar low risk of MS has been found in EBV-negative children.80,81 These children cannot be genetically resistant to EBV infection because they become infected later in life, as can be inferred by the fact that in the same population prevalence of EBV positivity increases from ~50% in childhood to ~95% in adulthood. After they become infected with EBV, if the infection results in mononucleosis, their risk of MS increases two- to threefold above the risk observed among EBV-positive individuals without a history of mononucleosis (Fig. 4).79,82,83 These data combined establish EBV infection as a strong risk factor for MS and indicate that the increased risk of MS among individuals raised in a more hygienic environment becomes manifest only after EBV infection (EBV variant of the hygiene hypothesis).79

The mechanisms by which EBV infection increases the risk of MS are still unclear.84 It seems likely that EBV predisposes to autoimmunity because a positive association has also been found with systemic lupus erythematosus.85 In a recent pathological study, strong evidence has been found of dysregulated EBV infection in the brain of most MS patients.86 If replicated, this
discovery may lead to a new era in MS research. To better understand the temporal relation between EBV infection and MS and the possible role of EBV, we have investigated longitudinally the antibody responses to different EBV antigens in healthy adults, comparing those who eventually developed MS with those who remained healthy. We found that individuals with MS experienced an elevation in antibody titers to the EBV nuclear antigen 1 (EBNA-1) many years before the onset of neurological symptoms, a result independently confirmed by others. Unexpectedly, this elevation does not have a clear temporal relationship with the time of MS onset; rather, the anti-EBNA-1 titers of individuals who will develop MS increase sometime between 20 and 30 years of age, and then remain elevated. EBNA-1 is a protein consistently expressed in latently infected B lymphocytes. A decline in anti-EBNA-1 titers is usually observed in immunosuppression, and antibodies to EBNA-1 tend to correlate with cellular immunity against EBV. In this context, it is interesting that CD4+ T cells specific to EBNA-1 are increased in frequency and recognize a broader range of epitopes in individuals with MS than in healthy controls. Also, two EBV peptides, one of which was from EBNA-1, have been recognized as targets of the immune response in the cerebrospinal fluid (CSF) of MS patients.

**Summary**

Overall, there is compelling evidence that EBV infection is a strong risk factor for MS. It is important to emphasize, however, that EBV infection by itself cannot explain some important aspects of MS epidemiology, and two are worth mentioning. One is the decrease in risk of MS with migration from high- to low-risk areas, and the other is the presumed occurrence of an epidemic of MS in the Faroe Islands. As discussed elsewhere, the migration data and the Faroe epidemics suggest that either EBV interacts with other infectious or noninfectious agents to cause MS, or that there are multiple strains of EBV with different propensity to cause MS.

**Implications for Prevention**

In the absence of an effective vaccine, there is not an obvious and feasible intervention that could contribute to MS prevention. Results of trials of antiviral drugs in MS did not support a strong beneficial effect. The solid data relating mononucleosis to increased MS risk suggest that some reduction in MS risk could be achieved by exposing children to EBV infection early in life. This conclusion, however, is far from certain, because, as discussed previously, infection with EBV early in life correlates with exposure to other infectious agents that could modulate the immune response to EBV, and the effect of anticipating age at EBV infection in the absence of exposure to other infectious agents remains unknown. Thus, the main implication is that there is a need to understand the mechanisms that explain the role of EBV in MS, because otherwise it may not be possible to translate the epidemiological evidence into preventive or therapeutic interventions.
CIGARETTE SMOKING

Although it does not contribute to explaining the geographical variations in MS incidence, there is strong and growing evidence that cigarette smoking is an important risk factor for MS. An association between smoking and MS risk was first found in an exploratory case-control study in Israel more than 40 years ago, and it has been confirmed more recently in case-control investigations and in a population-based survey. More robust evidence that smokers have a higher risk of developing MS than nonsmokers, however, is provided by the combined results of four longitudinal studies. Two of these investigations were conducted among women in the United Kingdom to determine whether use of oral contraceptives was related to MS risk. In both, women who regularly smoked were found to have a higher risk of MS; although, because of the small number of incident cases of MS (63 of 17,032 in one study, and 114 of 46,000 in the other), neither study convincingly demonstrates a significant increase. In the third investigation, which comprised more than 200,000 women and 315 incident cases of MS, there was a significant increase in MS risk among smokers, and a clear dose–response—the age-adjusted risk of MS among women who reported 25 or more pack-years of smoking was 70% higher than among those who never smoked (p < 0.01). This result was not materially changed after further adjustment for ancestry and latitude. Finally, a significant positive association between smoking and MS risk was found in a case-control study nested within the General Practice Research Database. When the results of these longitudinal studies are combined, the increasing risk of MS with increasing exposure to smoking becomes compelling (p < 0.001).

Although the possibility that this association is due to some factor that strongly affects both smoking behavior and MS risk cannot be excluded, there is no evidence that such a factor exists. Smoking may also adversely affect the progression of MS. An acute worsening of MS symptoms immediately following smoking was reported in a few clinical studies conducted more than 40 years ago and confirmed in later investigations. More recently, a significantly increased risk of transition to a secondary progressive phase of MS was reported among smokers with relapsing–remitting MS, as compared with nonsmokers.

Several hypotheses have been proposed to explain the increased risk of MS among smokers. These include vascular effects, effects on the immune system, increased production of nitric oxide, increased frequency of respiratory infections, and neurotoxic effects of cyanides and other components of cigarette smoke. The observation that smokers have an increased risk not only of MS, but also of other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and Graves’ disease, support a systemic effect on the immune system. On the other hand, nicotine or other components of cigarette smoke have effects on the integrity and function of the blood–brain barrier, affect cerebral circulation and signaling pathways in the CNS, and could potentially affect MS risk in multiple ways. A possible mechanism involves nitric oxide, which is present in cigarette smoke and also released in the brain in response to nicotine. Peroxynitrites, generated by the reaction of nitric oxide with superoxide, have been implicated in the pathogenesis of MS, and elevated CSF levels of nitric oxide metabolites were reported in individuals with MS and found to be associated with MS progression. Further research on the mechanisms relating cigarette smoke to MS risk and progression could be important not only for the immediate purpose of strengthening the evidence of a causal role of smoking, but also because it could lead to the discovery of new clues toward the prevention and treatment of MS.

Summary

There is strong evidence that smokers have a higher risk of MS than nonsmokers and suggestive evidence that smoking may also adversely affect MS progression. The increase in risk is ~70% among heavy smokers.

Implications for Prevention

Smoking cessation is likely to contribute to prevention of a substantial number of cases of MS. In the United States, ~20% of young adults are regular smokers. At the population level, the risk of MS due to smoking can be estimated as: [(1.5–1)/1.5]*0.20 = 6%, where 1.5 is the approximate RR of smoking on MS and 0.20 is the prevalence of smoking in the population. Therefore, if smoking was eliminated, up to 6% of the MS cases could be prevented. At the individual level, knowledge that smoking increases the risk of MS could be a strong deterrent, particularly for individuals who are at high risk of MS because of their family history.

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