

CAN SMOKING HAVE A POSITIVE EFFECT ON THE COURSE OF CERTAIN DISEASES? A SYSTEMATIC REVIEW

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A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Smoking cigarettes is a process during which many harmful substances are introduced into the lungs and the influence of these substances on the human body is not completely known. There are many diseases caused by smoking. Interestingly, there are also reports of positive consequences of smoking on some disorders.

Aim of the study: The purpose of this article is to review the literature in regards to the diseases in which cigarettes might have a paradoxically beneficial effect – both on the onset and their course. We also want to focus on the mechanisms responsible for this impact.

Material and Methods: Electronic searching of PubMed was performed. We analyzed articles published in the last 10 years with a particular emphasis on the most recent publications. Combinations of the following words were used: “smoking”, “nicotine”, and “autoimmune”. Publications were selected for reliability and non-bias.

Results: A total of 69 articles out of 2979 qualified for the review. Only studies involving humans were included. The positive effect of smoking cigarettes is observed especially in immunological diseases. It is possible that it is mediated by both stimulating and suppressing the immune system. It is assumed that cigarettes can reduce the risk of developing certain diseases. Smoking might also have an impact on the course of different comorbidities in the same patient.

Conclusions: There are many different mechanisms through which cigarette smoke and nicotine affect the human body. The harmful impact of these substances on one’s health has been demonstrated and their addictive component disqualifies them as remedies. Analysis of the mechanisms responsible for the beneficial effects of nicotine can lead to the search for new forms of therapy and prevention.

KEYWORDS: cigarette smoking, health, autoimmune diseases, nicotine

BACKGROUND

Cigarette smoking is among the most widespread addictions in Poland and worldwide [1]. A 2019 survey by the Centre for Public Opinion Research (CBOS) showed that a quarter of all Polish people smoke cigarettes. As much as a third of men stated that they have contact with cigarettes includ-

ing the 26% of men who smoke regularly. Women reported less contact with cigarettes, amounting to 21%, including 17% of women who are regular smokers.

The tobacco in a cigarette is subject to incomplete combustion causing the formation of several thousand harmful compounds which are inhaled into the lungs with the cigarette smoke [2]. Their effects on

one's health are unambiguously adverse. According to the World Health Organization (WHO), 8 million people died of diseases related to tobacco exposure throughout 2017. This addiction increases the risk of premature death by as much as three times [3], has been proven to contribute to the pathogenesis of several dozen diseases [3], and reduces one's quality of life [4]. The best-known consequences associated with cigarette smoking are lung cancer and chronic obstructive pulmonary disease, as well as cardiovascular diseases [5–7]. However, there are certain autoimmune diseases and skin diseases affected by the substances inhaled with cigarette smoke that can cause or modify the course of the given disease [8,9].

Due to the complex composition of cigarette smoke, it is difficult to determine its unambiguous effect on organisms. However, the fact that it stimulates the production of autoantibodies and inflammatory cytokines, as well as affects the generation of oxidative stress [10,11]. The effect of inhaled cigarette smoke on the immune system is complex [12]. Besides the aforementioned triggered pathological response of the immune system and their inflammatory effect, some authors claim they can have a protective and anti-inflammatory effect mediated through acetylcholine receptors [12]. Stimulation of this receptor pathway results in an increase in the response of regulatory T cells, a reduction in the levels of inflammatory cytokines, and apoptosis of inflammatory cells [12]. Cigarette smoking has the greatest effect on T and B cells but can also impact macrophages and natural killer (NK) cells – making it an intervention on both the innate and adaptive immune responses [13]. This effect on the immune system by stimulating and inhibiting it simultaneously is one of the mechanisms that could explain the fact that cigarette smoking might have a favorable effect on some diseases – both in terms of protection against the development of the disease and the alleviation of its course.

AIM OF THE STUDY

The goal of this article is to review the diseases for which there are reports concerning the potential paradoxically positive effects of cigarette smoking on their development and course. We also want to focus on the mechanisms responsible for this impact.

MATERIAL AND METHODS

The inclusion criteria used in the review were publication date, compliance with the foregoing topic, and reliability.

Eligibility criteria

We analyzed studies published within the last ten years with a particular emphasis on the most recent research.

Sample: Smokers, non-smokers, and ex-smokers suffering from diseases whose prognosis and course are positively related to smoking.

The phenomenon of interest: the positive effects of cigarette smoking on certain diseases.

Evaluation: Any patient reporting will be evaluated.

Design: All kinds of observational studies: cohort, case control, and individual case studies.

Research type: One can search for qualitative, quantitative, and mixed studies.

Search strategy

The search was conducted using the PubMed Database. The last time the source texts were reviewed was on 1/03/2022. Keywords such as “smoking”, “nicotine”, and “immunological diseases” were used.

Data collection process

Studies were divided into groups relating to specific diseases. Each of the three authors reviewed selected scientific articles for inclusion in the review. Each of the authors worked independently. First, abstracts were read, and then full articles for selected studies. The extracted data included the following information: the impact of smoking on the course or risk of diseases, the impact of passive smoking, or the impact of smoking in the past. The risk of bias for each study was assessed independently by the

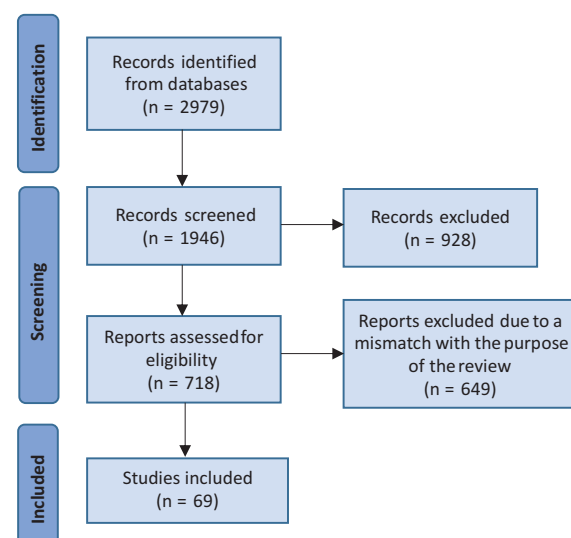


Figure 1. The search process

same authors. The third author will help settle any disputes. The collected data will be presented in text form to allow for a thorough understanding of the topic under discussion.

RESULTS

Study selection

At first, 2979 articles were found and 69 were qualified for review as some studies did not meet the

inclusion criteria after reviewing the abstract. Some studies that appeared to meet the inclusion criteria were excluded due to dishonesty or bias. The search process is presented in Fig. 1.

Discussion

UC is a chronic disease from the group of inflammatory bowel diseases. Its etiology has multiple factors including environmental, genetic, and immunological factors [13]. It is probably one of the best-known diseases in which cigarette smoking has

Table 1. Study characteristics

Study	Study design	Patients	Country	Observations
Park S et al. (2019) [14]	Retrospective cohort study	23,235,771	South Korea	Compared with nonsmokers, former smokers had a significantly higher risk of ulcerative colitis (UC) development.
Higuchi LM et al. (2012) [15]	Prospective cohort study	229,111	United States	Current smoking is associated with an increased risk of Crohn's disease, but not UC.
Khalili H et al. (2015) [16]	Prospective case-control study	121,700 116,430	United States	Smoking may influence the levels of androgens in women and the risk of UC.
Ng SC et al. (2015) [17]	Case-control study	442 incident cases and 940 controls	8 countries in Asia and Australia (Asia-Pacific)	Ex-smoking increased the risk of UC.
Blackwell J et al. (2019) [18]	Retrospective cohort study	9,616	United Kingdom	Smokers and never-smokers with UC had similar outcomes with respect to flares, thiopurine use, corticosteroid dependency, hospitalization, and colectomy.
Van der Heide F et al. (2009) [19]	Retrospective cohort study	675	Netherlands	In UC, active smoking shows dose-dependent beneficial effects.
Brenner S et al. (2001) [20]	Case-control study	126 pemphigus patients and 173 healthy controls	Bulgaria, Brazil, India, Israel, Italy, Spain, and the USA	The risk for pemphigus vulgaris was lower for ex-smokers and current smokers than for patients who had never smoked.
Valikhani M et al. (2007) [21]	Case-control study	210 pemphigus patients and 205 control subjects	Iran	Smoking has a protective factor in pemphigus.
Servioli L et al. (2019) [22]	Population-based cohort study	106	United States	Current smokers were less likely to have progressive systemic sclerosis (pSS).
Olsson P et al. (2017) [23]	Case-control study	63	Sweden	Current smoking was associated with a reduced risk in the subsequent diagnosis of pSS.
Stone DU et al. (2017) [24]	Case-control study	1,288	United States	Protective effects of tobacco on pSS manifestations.
Mofors J et al. (2020) [25]	Case-control study	815 patients and 4,425 controls	Sweden	Individuals who develop pSS smoke as much as the general population during early life but are more likely to have stopped.
Bartoloni E et al. (2015) [26]	Retrospective population-based cohort study	1,343	Italy	Smoking was less prevalent in women with pSS than in control subjects.
Manthorpe R et al. (2000) [27]	Prospective cohort study	300	Sweden	Cigarette smoking is negatively associated with focal sialadenitis-focus scores > 1 in lower lip biopsies in patients with primary Sjögren's syndrome.
Ungrasert P et al. (2016) [28]	Case-control study	345 patients and 345 controls	United States	Current smokers have a lower risk of developing sarcoidosis.
Newman LS et al. (2004) [29]	Case-control study	706	United States	A negative association between tobacco smoking and sarcoidosis risk.
Hattori T et al. (2013) [30]	Retrospective cohort study	388	Japan	There could be various relationships between smoking and the development of sarcoidosis in different populations.
Rivera N V. et al. (2019) [31]	Case-control study	3,713	Sweden	Sarcoidosis risk is modulated by smoking due to genetic susceptibility.

Table 1 contd.

Study	Study design	Patients	Country	Observations
Janot AC et al. (2015) [32]	Retrospective cohort study	109	United States	Tobacco exposure is an independent risk factor for ocular sarcoidosis.
Pérez ERF et al. (2013) [33]	Retrospective cohort study	142	United States	This study supports the harmful effects of cigarette smoking on chronic hypersensitivity pneumonitis (HP).
Mooney JJ et al. (2013) [34]	Retrospective cohort study	177 patients with HP and 224 patients with idiopathic pulmonary fibrosis (IPF)	United States	If HP develops in a cigarette smoker, it is more often chronic than in non-smokers and has a higher risk of death.
Wang P et al. (2017) [35]	Prospective cohort study	119	China and United States	No connection between cigarette smoking and the survivability of HP.
Ojanguren I et al. (2019) [36]	Prospective cohort study	160	Spain	No connection between cigarette smoking and the survivability of HP.
Lee YB et al. (2019) [37]	Retrospective nationwide population-based study	22,995,024	Korea	Decreased incidence of Behçet's disease (BD) in current smokers.
Malek Mahdavi A et al. (2019) [38]	Case-control study	192 patients with BD, 822 healthy siblings of patients with BD, and 373 controls	Iran	Smoking is not a significant risk factor for BD.
Lapi F et al. (2016) [39]	Retrospective population-based study	Almost 1 million	Italy	A protective effect of cigarette smoking on the risk of developing chronic spontaneous urticaria.

a potentially favorable effect, although this connection is not clear [40]. There are reports showing fewer smokers among UC patients than in control groups identifying the avoidance of smoking as a risk factor for the development of UC [14,41,42]. It is also possible that smoking is only a protective factor in men [14,15]. A probable cause for such an impact on only one sex may be related to the effect smoking has on the levels of sex hormones [16,43]. Former smokers are at a higher risk than people who have never smoked or are current smokers – the risk of developing UC in former smokers increases with the duration of the previous exposure to cigarettes [14,15,17]. The effect of cigarettes on the reduced risk of developing the disease has been best-proven, yet the “curative” effect of cigarettes on the course of an already existing disease is controversial. The available research in this regard is contradictory. There are reports that cigarette smoking does not significantly reduce the risk of exacerbations or reduce the frequency of hospitalization. In addition, smoking has not shown to affect the proximal colon less frequently or reduce the necessity of thiopurine treatment or colectomy [18,40]. Simultaneously, according to some researchers, current cigarette smokers may have a reduced risk of colectomy and a reduced necessity for the escalation of their current pharmacological therapy [19,44]. Due to the complex composition of cigarette smoke, it is difficult to pinpoint the mechanism responsible for its protective effects in UC. Cigarette smoke may be responsible for changes in the intestinal microbiome and an increase in the thickness of the in-

testinal mucus layer. Additionally, cigarette smoke reduces the activity of the innate immune response which plays the greatest role in protecting against the development of the disease [42]. It should be emphasized that the effects of the stimulant under consideration on the course of Crohn's disease – another member of the group of inflammatory bowel diseases – are completely different and considered adverse [41,45].

Pemphigus is an autoimmune disease involving the skin and mucous membranes causing blisters and erosions. Many types of pemphigus are described, but the most important ones include pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus [46]. As with UC, most studies on pemphigus (both vulgaris and foliaceus) report a smaller percentage of smokers than in the control group [47]. This shows that cigarette smoking may be deemed a protective factor against pemphigus occurrence [20,48]. According to some studies, its effect was more significant in men than in women [20,21]. Research determining the effect of cigarettes on the locations of pathological changes was conducted, however, it is inconclusive on their impact in this regard [49]. In both smokers and non-smokers, the most prevalent type of pemphigus is the form involving both mucous membranes and skin [49]. Faster remission was observed among smokers for pemphigus vulgaris [49]. Additionally, in the same study, remission after one year of treatment was obtained in a significantly larger number of smokers than in those avoiding tobacco [49]. However, the research in this regard is insuffi-

cient and needs to be deepened to enable the drawing of an unambiguous conclusion. The mechanism responsible for the described effects of cigarette smoke has not been precisely discovered so far. The stimulating effect of nicotine on the acetylcholinergic receptors present on keratinocytes is suspected to be of greatest significance [50].

Sjögren's syndrome is a chronic autoimmune disease characterized by the accumulation of lymphocytic infiltrations in exocrine glands resulting in their failure. There are two types of this syndrome: pSS and secondary (developing in the course of other diseases, mostly rheumatological) [51]. A lower percentage of cigarette smokers have been observed in many studies involving pSS patients [22]. Additionally, the status of being a former smoker has a higher risk of disease development [23,24]. A study was conducted in which the frequency of cigarette smoking in early youth was observed among pSS patients to be the same as in the control group, but this percentage decreased with aging patients who later developed pSS [25]. This might suggest a protective effect of cigarettes or suggest that the early emergence of discrete symptoms of the disease, even before the diagnosis, leads patients to change their habits and quit the addiction. Stone et al. [24] point out that the duration of tobacco exposure is significant and inversely proportional to the risk of developing pSS. There are also reports that smoking reduces levels of anti-Ro and anti-La antibodies [26]. However, this claim demands further research, since, according to Servioli et al. [22], cigarette smoking or lack thereof was unrelated to the impact on the levels of antinuclear, anti-SSA, and anti-SSB antibodies, as well as rheumatoid factor. Similarly, Manthorpe et al. [27] reported a lack of differences in tobacco smoking habits between pSS patients and the control group. However, during the biopsy of labial salivary glands utilized in the diagnosis of Sjögren's syndrome, the same study showed that tobacco smoking resulted in a smaller number of detected inflammatory foci in the biopsied material.

Sarcoidosis is a generalized granulomatous disease. It manifests itself usually by hilar lymph node enlargement and changes in the lungs [52]. Its etiology is unknown, yet there are studies showing that smokers are less at risk of developing sarcoidosis [28,29,53]. Again, in cases of this disease, the cause of such a relation is unclear. The already described positive effect of cigarette smoke on the suppression of T cells and macrophages may constitute the basis of this mechanism. Furthermore, through its effect on these cells, cigarette smoke may disrupt the process of granulomata formation [54]. On the other hand, a study conducted in Japan showed a higher percentage of smokers among sarcoidosis patients

than in Western civilizations which might indicate the presence of additional (e.g. environmental) factors modulating the protective effect of nicotine [30]. A study by Rivera et al. [31], suggests that cigarette smoking may influence the development of sarcoidosis through gene modulation. On the other hand, Janot et al. [32] reported that cigarette smoking may be a risk factor for the development of the ocular form of sarcoidosis. It should be stressed that the reports are ambiguous and the effect of cigarettes on the development of the disease under consideration requires more thorough studying.

HP is a group of diseases resulting from repeated inhalation exposure to chemical compounds or organic particles, causing an immunopathologic response and lung damage in a predisposed person. An acute and chronic form has been described [55]. According to some reports, HP develops less frequently among cigarette smokers, however, studies in this regard have been published many years ago and are in need of updating [56,57]. Researchers suspect that the protective effect of nicotine consists mainly in the suppression of pulmonary macrophages [56]. However, it should be emphasized that if HP develops in a cigarette smoker, it is more often chronic than in non-smokers and entails a higher risk of death [33,34]. Simultaneously, studies have been performed in which no connection between cigarette smoking and the survivability of HP was confirmed [35,36]. On the other hand, due to the increased popularity of electronic cigarettes, severe cases of HP have been observed in recent years caused by the exposure (active and passive) to the e-cigarette aerosol [58,59]. E-liquids are artificially aromatized and rich in a range of substances that may be irritating to the airways [60]. Therefore, these cannot be considered a healthier alternative to traditional cigarettes.

Cigarette smoking may also play a role in other diseases, however, the available research is scant in this regard. There are studies indicating the possible protective effect of cigarette smoke in BD, yet others that mention smoking among the risk factors for developing the disease [38,61,62]. Some reports state that although smoking has no significant impact on the development of the disease and the manifested symptoms, the activity of the disease in smokers was higher at the moment of diagnosis [38]. A study by Lapi [39], suggests the protective effect of cigarette smoking on the risk of developing chronic spontaneous urticaria, yet this claim requires further research. The topic on the potential neuroprotective effects of nicotine was also raised in some studies in the context of protection against the development of Parkinson's syndrome [63–65].

Treatment of UC or sarcoidosis using nicotine has been attempted [66,67]. V. Kannichamy

et al. [68] analyzed the reports regarding the effects of nicotine treatment in the form of transdermal patches on mild and moderate forms of UC. Nicotine combined with conventional treatment was more efficacious than conventional therapy alone, however, this claim demands newer and better-controlled studies. Due to its undesirable effects, nicotine should only be introduced into the treatment of patients who do not react to standard methods [69]. Simultaneously, the activation of the cholinergic pathway triggered by nicotine is emphasized, meaning its neuroprotective and anti-inflammatory potential could be utilized in the search for a selective nicotine receptor agonist devoid of the unfavorable effects of nicotine [66,70]. Therefore, the processes described above and their effect on individual diseases may serve as a starting point for the analysis of mechanisms responsible for the observed favorable effects of nicotine and the search for new forms of therapy or disease prevention.

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Limitations

Overall, there is not enough hard evidence to say that the effects of cigarette smoking are positive for certain diseases. Some studies have assessed a small number of patients or have not followed patients for long enough. It is necessary to conduct more detailed research on this topic, which will allow the drawing of broader conclusions.

CONCLUSIONS

The complexity of the effect of cigarette smoke and nicotine contained therein is very interesting, yet it's addictive and unhealthy nature places it in an unambiguously negative light. Cigarette smoking is highly harmful in many aspects, affecting many organs and systems. Therefore, it is obvious that tobacco smoking should not be recommended for the prevention of the diseases described above.

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