Beneficial effects of nicotine and cigarette smoking: the real, the possible and the spurious

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Cigarette smoking is an established risk factor for cancer and cardiovascular disease, and is the leading cause of avoidable disease in most industrialized countries. Less well-known are possible beneficial effects, which are briefly considered in this survey.

Preliminary data suggest that there may be inverse associations of smoking with uterine fibroids and endometriosis, and protective effects on hypertensive disorders and vomiting of pregnancy are likely. Smoking has consistently been found to be inversely related to the risk of endometrial cancer, but cancers of the breast and colon seem unrelated to smoking. Inverse associations with venous thrombosis and fatality after myocardial infarction are probably not causal, but indications of benefits with regard to recurrent aphthous ulcers, ulcerative colitis, and control of body weight may well reflect a genuine benefit. Evidence is growing that cigarette smoking and nicotine may prevent or ameliorate Parkinson's disease, and could do so in Alzheimer's dementia. A variety of mechanisms for potentially beneficial effects of smoking have been proposed, but three predominate: the 'anti-estrogenic effect' of smoking; alterations in prostaglandin production; and stimulation of nicotinic cholinergic receptors in the central nervous system.

Even established inverse associations cannot be used as a rationale for cigarette smoking. These data can be used, however, to clarify mechanisms of disease, and point to productive treatment or preventive options with more narrowly-acting interventions.

It is evident from other papers in this symposium that cigarette smoking is a potent health hazard, almost certainly the leading avoidable cause of mortality and morbidity in most industrialized countries. The health burden of smoking is largely due to well-established increases in the risk of serious chronic disorders, including coronary artery disease and stroke, chronic lung disease, and many cancers[1]. Less well-known are suggestions that cigarette smoking might actually confer some beneficial effects in certain circumstances. This review surveys the conditions for which some benefits have been claimed, and considers briefly the evidence in support of these possible benefits.

Gynecological and obstetric conditions and events

Cigarette smoking has been noted to have an 'anti-estrogenic' effect, since women who smoke cigarettes behave as though they were relatively estrogen-deficient[2,3]. This effect would be expected to have a beneficial impact on diseases and processes associated with estrogen excess, and several of the gynaecological and obstetric conditions that have been proposed to be inversely related to cigarette smoking are thought to be the consequence of estrogenic stimulation.

Uterine fibroids and endometriosis

In many regards, the presence of fibroids reflects estrogenic influences: women who are lean or postmenopausal have a lower prevalence of these tumours[4,5], although oestrogen replacement therapy has only inconsistently been related to risk[4,6]. Available data also suggest that smoking may be inversely related to the risk of having fibroids[4–6], with heavy smokers having about half the risk of never smokers, even after control for covariables such as age, body weight, and menopausal status.

Endometriosis is another disorder that seems to respond to estrogenic stimuli, and has been inversely related to cigarette smoking in several studies[7–9]. Initiation of the habit at an early age may be required for this effect, although the available data are insufficient to clarify this point.

Effects during pregnancy: nausea/vomiting and hypertensive disorders

Vomiting of pregnancy is the third oestrogen-related condition[10] that has been noted to be less common in smokers than in non-smokers[e.g.10–13]. However, the data are not conclusive: the possibility of confounding has not been extensively considered, and adjusted relative risk estimates have not been consistently less than 1.0[14,15].

A lower incidence of hypertensive disorders of pregnancy among smokers has been regularly found. Pre-eclampsia and eclampsia have been investigated in several studies, and a 30–50% reduction in risk has been reported among smokers[e.g.16–21]. Although early studies did not control for confounding, this has been done in the more recent investigations, with essentially no effect on the risk estimates. Smoking during the second half of pregnancy may be the most relevant exposure[18]. Gestational hypertension is also less common among smokers than among non-smokers, although the effect is somewhat less pronounced than for pre-eclampsia/eclampsia[16,18,22–24].

The mechanisms that could explain an effect of smoking on hypertensive disorders of pregnancy are not clear. Several possibilities

have been proposed, including inhibition of thromboxane production, limitation of plasma volume expansion during pregnancy, and hypotensive effects of the thiocyanate contained in cigarette smoke[21].

Dysmenorrhea

One report that cigarette smokers have less dysmenorrhea compared with non-smokers[25] prompted speculation that inhibition of prostaglandin production might explain the reduced pain[26]. Other investigations, however, have reported no association, or (more commonly) increased dysmenorrhea among smokers[e.g.27–31]. Thus the data actually suggest an increased risk among smokers.

Down syndrome

Several studies have reported that smoking mothers have a reduced risk of delivering an infant with Down syndrome compared with non-smoking mothers[32,33]. However, in some of these investigations there was inadequate control for maternal age, and other studies reported no association, or only a weak one[34,35]. Currently, the issue remains unresolved.

Neoplasia

Tobacco and cigarette smoke are clearly rich sources of carcinogens, and greatly increase the risk of cancer at virtually all anatomic sites having direct contact with tobacco or tobacco smoke, as well as at some sites that lack such contact[36]. There have also been suggestions that smoking might have an inverse relationship with the risk of neoplasia at some locations that do not have smoke contact—where direct carcinogenesis is not an issue, and where other effects of smoking might play a protective role.

Fibrocystic breast disease and breast cancer

Fibrocystic breast disorders are a heterogenous group of processes in the breast that appear to be responsive to ovarian hormones[37]. Several studies have suggested a lower risk among smokers, especially among currently smoking postmenopausal women[6,38,39]. The data are not consistent, however, and in other analyses no association was found[40].

A few investigations have suggested that cigarette smoking may be inversely related to the risk of breast cancer[41]. These were largely

case-control studies, and subsequent investigations have reported no association or even a small increase in risk[2,42,43]. Apparently, the original reports were chance findings, or possibility the result of biasing factors in the studies themselves[44]. The considerable data available on the topic indicate that there is no substantial association, either overall, or among premenopausal or postmenopausal women considered separately[2,42,43].

Endometrial cancer

Endometrial cancer is the only malignancy that has repeatedly been shown to be inversely related to cigarette smoking[2,45]. The association is stronger among postmenopausal women, and seems to be absent in former smokers. A dose–response pattern has been found in several studies, with a relative risk of 0.5 or less among heavy smokers in comparison to never smokers. The association remains even after control for the effects of lower body weight and earlier age at menopause in smokers. In some studies, but by no means all, the association was particularly marked among women taking exogenous estrogens[2,45], a pattern consistent with the hypothesis that smoking may be acting to alter the metabolism of oral estrogens.

Colorectal cancer

Some reports have suggested that cigarette smoking may be inversely related to the risk of colorectal cancer[e.g.46,47] — in particular colon cancer among women[47]. However, other epidemiological studies have not confirmed this association[48,49], or have reported an increased risk among long-term smokers[50]. Although the possibility of an increased risk remains controversial, the available data clearly do not suggest that smoking has an inverse association with colon cancer.

One investigation reported that among patients with ulcerative colitis, cigarette smokers had a lower risk of bowel cancer than non-smokers[51]. The association was not statistically significant, however, and the issue has not been extensively studied; the suggestion remains a speculative one.

Cardiovascular Disease

Survival after myocardial infarction

Several studies have suggested that cigarette smokers have a lower case fatality after myocardial infarction than non-smokers (reviewed in[52]), with a reduction in fatality of 40% or greater in some reports. Several

explanations for this association have been advanced, including differences between smokers and non-smokers in the types of arterial lesions that precipitate infarction, the beneficial effects of the smoking cessation enforced by hospital admission, and confounding by other prognostic factors. The last possibility is almost certainly part of the effect; strong associations between smoking and potent prognostic factors have been demonstrated[e.g.52], and in many reports on the topic the control for confounding—even by age—has been inadequate.

Venous thrombosis

In the 1970s, there were several reports that smokers had a lower risk of deep venous thrombosis after hospital admission for myocardial infarction[53–55], gynaecological surgery[56] or other reasons[57]. The relative risks that can be computed from the data presented are strikingly low: 0.25 or lower. Some later data were similar[58], but most of these studies did not consider possible confounding, even by age. Other, often more formal, studies have failed to confirm the finding[59–63]. However, these negative studies have focussed on slightly different clinical events than the ones that suggested a benefit. All were conducted among women, and none focussed on in-patient venous thrombosis, as did the earlier reports. The literature regarding pulmonary embolism provides some clarification: there are no suggestions of protective effect of smoking, although the data are not extensive[64–66].

In many ways, an anti-thrombotic effect of cigarette smoking would seem implausible; smoking is generally thought to exert a pro-coagulant effect through increased fibrinogen levels, reduced fibrinolysis, and probably through platelet activation[67–69]. However, there is *in vitro* evidence that nicotine and cotinine can inhibit synthesis of prostaglandins, including thromboxane, a potent proaggregatory prostanoid[68,70–72]. These direct prostaglandin-inhibiting effects of nicotine could conceivably lead to a decreased risk of thrombosis, although it remains to be demonstrated that these *in vitro* effects have *in vivo* clinical significance.

Inflammatory and immunological disorders

Cigarette smoking has been shown to affect several measures of immune functioning, including those of T-cell functioning and antibody response[73]. The usual concern is that this immune suppression may lead to a susceptibility to infections, although it is conceivable that the impairment could be beneficial for immunologically-mediated disorders.

Aphthous ulcers

An inverse association between cigarette smoking or smokeless tobacco use and the risk of recurrent aphthous ulceration of the oral mucosa has been reported in several studies, though not in all[e.g.74–77]. Some investigators have also published case reports noting a worsening of the ulcers after smoking cessation, with relief after resumption[e.g.78,79]. It has been proposed that the increased oral keratinization associated with tobacco use could explain the inverse association; the possible efficacy of nicotine chewing gum suggests that nicotine is an active moiety[80].

One study reported that another oral disorder, herpes labialis, is less prevalent in tobacco users than in non-users[81]. However, the differences were small, confounding was not considered, and the finding seems not to have been confirmed.

Ulcerative colitis

An inverse association between cigarette smoking and ulcerative colitis has been repeatedly documented. The relationship is complex, since current smokers have a markedly reduced risk relative to never smokers (as low as 0.4 or lower), but former smokers have, if anything, an increased risk[82,83].

Reports of the amelioration of ulcerative colitis symptoms by smoking[e.g.84] or nicotine administration[85,86] led to formal trials of transdermal nicotine. The pattern of response resembles that of corticosteroid therapy: transdermal nicotine aided the treatment of patients in relapse[87], but a somewhat less intense nicotine regimen was ineffective in prolonging remission[88].

Thus there is considerable evidence that smoking—and nicotine in particular–has a beneficial effect in ulcerative colitis. The effect remains unexplained, although several mechanisms have been proposed, including changes in bowel mucus or prostaglandins, immune suppression, and other effects in the bowel[89].

Extrinsic allergic alveolitis

Smoking seems clearly to be inversely related to extrinsic allergic alveolitis (farmers' lung, pigeon breeders' lung), a chronic immunologically-mediated lung disorder. Several studies have noted an inverse association of cigarette smoking with the clinical syndrome[90–93], and numerous investigations have documented that serum antibodies to the

antigens associated with the disorder are reduced[e.g.73,91,92,94–96]. The suppressive effect of smoking on antibody levels may be reversible, since former smokers seem to have antibody levels intermediate between current smokers and never smokers[91,92,94,96].

Hay fever and atopy

A lower prevalence of hay fever was noted among smokers in one study[97] and other reports have found that smokers are less likely to react to skin prick testing with common seasonal antigens[98–100]. Reactions to occupational antigens, however, seem to be enhanced[100]. Aside from the need for clarification of these discrepant findings, there is at least one issue that hampers interpretation of these data: it is not clear if smoking impairs the immune response related to atopy, or if atopic individuals have difficulty even starting to smoke because of allergic symptoms.

Sarcoidosis

Several case-control studies have reported an inverse association between smoking and the risk of sarcoidosis[101–106]. However, the control groups used by many of these investigations do not closely correspond to the cases, and it is possible that selection bias may have distorted the findings. Also, some negative reports have been published[90,107], and the possibility of confounding by social class has explicitly been raised[107]. The association thus remains uncertain, although the effects of smoking on lymphocyte populations make it plausible[104,105].

Acne

One study with clinic cases and general population controls reported an inverse association between cigarette smoking and severe acne[108], a finding which has been ascribed to impaired inflammatory responses in smokers[100]. No other evidence regarding the association seems to be available.

Metabolic effects

Body weight

An inverse association between cigarette smoking and body weight is well established[109,110]. The weight difference between smokers and non-smokers appears to be larger at older ages, and is most marked for

moderate smokers. Cessation of smoking is associated with weight gain, a factor which impedes smoking control efforts. Animal data support the association[110].

Several possible mechanisms have been advanced for the effects of smoking on body weight[109,110]. Laboratory data and prospective studies suggest that smoking is associated with a decreased caloric intake, although cross-sectional investigations tend not to confirm this[110]. In any case, the effect of smoking is not completely explained by differences in energy intake or physical activity; several studies have shown that cigarette smokers have a higher metabolic rate than non-smokers[111–113]. Most of the weight-reducing effects of smoking seem to be due to nicotine, although there are suggestions of a behavioral component as well[113].

Central nervous system functioning

There are several reasons why an effect of cigarette smoking or nicotine administration might plausibly have an effect on the functioning of the central nervous system. Nicotinic cholinergic receptors are widespread in the brain[114] and chronic nicotine administration increases their density[115]. Presumably as a consequence of stimulation of these receptors, nicotine leads to the release of several neurotransmittors with potentially important functional consequences[116].

Motor system disorders: Parkinsonism and Tourette's syndrome

An inverse association between cigarette smoking and Parkinson's disease is well established[117–119]. Numerous epidemiological studies have confirmed the apparent protective effect, with ever smokers having a relative risk about 0.5 in comparison to never smokers. Although most of the research has involved case-control study of prevalent cases, cohort investigations and mortality studies have also supported these findings. In aggregate, the data overcome most biases that have been proposed to explain the association[117–119]. However, the possibility that individuals destined to be at high risk for Parkinson's disease may have an aversion to smoking has not been completely excluded.

The inverse relationship of smoking with Parkinson's disease may well reflect a genuine biological effect. Some animal studies, but not all, have shown that cigarette smoke or nicotine can ameliorate experimental Parkinsonism[120–123]. Also, some case reports and a more formal double-blind trial have suggested a benefit of nicotine administration in patients

with Parkinsonism[124,125]. Moreover, nicotine appears to effect several disorders of the extrapyramidal motor system in addition to Parkinson's disease: smoking or nicotine can reduce drug-induced Parkinsonism, ameliorate Tourette's syndrome, and worsen neuroleptic tardive dyskinesia, effects that all point to effects on dopaminergic motor systems[119,126].

Alzheimer's disease

The epidemiological data regarding a possible inverse association between cigarette smoking and Alzheimer's dementia is fairly consistent; most studies have reported an inverse association, although there are reports to the contrary[118,127,128]. As for Parkinson's disease, much of the research involves case-control studies with prevalent cases. Alzheimer's epidemiology is complicated by the difficulties of distinguishing Alzheimer's dementia from other dementing illnesses, and (in case-control research) by the need for surrogate respondents. However, the plausibility of a protective effect of smoking on Alzheimer's disease is supported by reports that short-term nicotine administration may provide modest improvements in measures of mental functioning in patients with Alzheimer's disease[129,130].

Mental functioning

In addition to effects in Parkinson's disease and Alzheimer's dementia, smoking may also effect mental performance in non-diseased individuals. Research conducted among smokers has shown that cigarette smoking (or nicotine administration) has several benefits, including modest improvements in vigilance and information processing, facilitation of some motor responses, and perhaps enhancement of memory[131–133]. Also, smoking or nicotine clearly ameliorates the mild deterioration in mental functioning associated with nicotine withdrawal. The effects of nicotine in non-smokers are not as clear. The use of smokers in much of the cognitive research has necessarily involved individuals with chronic nicotine exposure; this may well alter acute affects through tolerance or receptor changes, or through the distortions associated with nicotine withdrawal. Nonetheless, there are certainly data suggesting benefits of nicotine in non-smokers with regard to performance and information processing[131–135]. Consistent with these findings, experimental studies in animals have suggested that nicotine may improve learning and memory, although some investigations showed evidence of nicotine-associated impairments[132].

Mechanisms

A variety of mechanisms have been invoked to explain the relationships described. Several of the proposed beneficial effects involve disorders that are associated with estrogen-excess (endometrial cancer, uterine fibroids, endometriosis, fibrocystic breast disease). The anti-estrogenic effect is itself unexplained, but may involve induced changes in the metabolism of estrogens, direct toxic effects on ovarian follicles, or interference with pituitary regulation of sex hormone systems[2]. A second group of possible benefits involves the effects of smoking on central nervous system neurotransmitter systems[116]. These effects could plausibly explain associations of smoking with Parkinson's disease, Alzheimer's dementia, and mental functioning. Third, there are clear indications that smoking can alter prostaglandin pathways, and suppress at least some aspects of immunological functioning[68,73]. These effects could underlie the associations of smoking with ulcerative colitis, farmers' lung and hypertensive disorders of pregnancy.

These benefits are not without their costs, however. The antiestrogenic effect of smoking may at least partially explain the association of smoking with an increased risk of osteoporotic fractures[2] and the central nervous system effects of nicotine clearly underlie tobacco dependence[109]. Inhibition of prostaglandin synthesis is thought to play a role in the effects of smoking on vascular disease[67].

Conclusions

Some of the proposed beneficial effects of smoking are not real. The effect of smoking on survival after myocardial infarction is at least partly artifactual, and smokers do not have a lower risk of dysmenorrhoea, colorectal cancer, and breast cancer as has been suggested. For effects on Down syndrome and venous thrombosis, the available data are not sufficient for conclusions to be drawn, and the association remains speculative; no convincing mechanisms have been proposed. For other conditions, possible benefits are more plausible, but remain unproven. These include functionally important improvements in mental functioning and Alzheimer's dementia, and inverse associations with sarcoidosis. Finally, the available evidence is very suggestive of a genuine benefit with regard to endometrial cancer, aphthous ulcers, ulcerative colitis, external allergic alveolitis, Parkinson's disease, and control of body weight.

These associations can hardly be used to justify cigarette smoking; its adverse effects are simply too overwhelming. However, these data do provide insight into the mechanisms of several diseases, and suggest avenues for treatments and preventive measures that are likely to be far safer than cigarette smoking.

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