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**Review Article**

# Smoking and Gut

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**Smoking has not only enormous deleterious effects on cardiovascular, cerebral, and bronchial organs but also profoundly alters the function of all parts of the gastrointestinal tract through various mechanisms. Except the sole curiously observed benefit of smoking on the course of ulcerative colitis, it increases the prevalence of the common gastrointestinal diseases namely gastroesophageal acid reflux, peptic ulcer, and Crohn's diseases. It also increases the incidence of cancer of oral cavity, esophagus, stomach, pancreas, and liver mostly in a dose-response relationship and worsens the prognosis of colon cancer. The cessation of smoking is associated with the reduced incidence of cancer in the reported organs, but its effect on the regression of benign disease is not generally studied. The physicians must be aware not only of the harmful effect of smoking on the cardiovascular and bronchial systems, but also about the detrimental consequences of life-long smoking on the gastrointestinal tract and the increase of its benign and malignant diseases.**

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## Introduction

The seeking of various abuses is an inherent human behavior. Nicotine consumption fulfills this need. About 20% to 30% of population in all countries are affected by nicotine use. Since more than 50 years ago, the deleterious effects of smoking on various organs and health are emerging and the general awareness is increasing. The enormous financial burden of nicotine consumption on health disorders has made the policymakers of many countries to implement laws to ban smoking in public places, especially by young adults, in schools, governmental offices, and in the aerial and ground transporting tools and restaurants.

An average cigarette contains 6 – 12 mg nicotine. It delivers 1 – 3 mg nicotine systematically. Eighty to ninthy percent of nicotine is altered in the body and metabolized in the liver to cotinine as its main metabolite.[1]

Nicotine acts on different nicotinic cholinergic receptors in ganglia and brain, whereby acetylcholine and catecholamine and various hormones are released. These mediators affect various systems and organs. The chronic intake of nicotine increases the density of the nicotine receptors.[2] The immune system and inflammatory function may be involved by long-term smoking.[3] The constituents of smoke such as carbon monoxide may increase sympathetic outflow,[4] impair delivery of oxygen by increase of carboxyhemoglobin level,[5] decrease mitochondrial respiration,[6] induce severe endothelial injury,[7] and oxidant injury.[8] These are some mechanisms affecting the pathophysiology of organ systems in long-term.

Among the many organs affected by the nicotine abuse, the most gastrointestinal (GI) tract represents the important target for various diseases developed by different mechanisms of effects not related with the promotion of atherosclerosis. In the GI tract, acute absorption of nicotine by the parasympathetic ganglia and cholinergic nerve endings results in increased tone and motor activity of the bowel inducing nausea and diarrhea in those who have not been exposed to nicotine previously; however, by continuous exposure, the long-term effect changes the GI

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motility, the multiple secretory, and barrier function of the intestinal tract and release of hormones and mediators affecting the structural integrity of the epithel and mucosa. The objective of this review was to describe the different mechanisms involved in the pathogenesis of smoking-induced disorders and to study the various GI diseases affected by long-term smoking based on the relevant publications performed during the last decades.

**Benign oral diseases**

The unpleasant oral odor of smokers causes the separation of smokers from nonsmokers in family and in establishing nonsmoking areas in state and healthcare facilities and open places or the complete prohibition of smoking outside the own milieu. The policymakers are divided according to their ambition to ratify the corresponding laws for such intense limitation.

Besides the bad odor, tobacco use affects the surface epithelium of the tongue and gingiva, resulting in changes in the appearance of the tissues, the development of black hairy tongue, the nicotine stomatitis, keratosis, melanosis, periodontal diseases, darkening of teeth, and tooth abrasion.[9 – 13]

Another study has shown that oral diseases and periodontal disorders are mostly and closely related to the poor oral hygiene by smokers and not directly to smoking itself.[14]

**Pathophysiology of esophagus in smokers**

There are many studies revealing a 19 – 42% diminution in cardia sphincter tone in smokers as compared to nonsmokers.[15–20] Cigarette smoking relaxes the cardia sphincter and is associated with increased rate of reflux episodes and heartburn.[21–22]

There are some evidence that unlike in nonsmokers which acid content of the lower esophagus is neutralized and cleared rapidly, in smokers it takes a longer time. For instance, in asymptomatic chronic smokers, after 12 hours of abstinence, a mean of only 10.7 swallows was required to clear a 15- mL bolus of 0.1 N hydrochloric acid from esophagus; immediately after smoking, however, a mean of 20.9 swallows was required to clear the bolus.[23]

Smokers have not only prolonged clearing time for acid in esophagus compared to nonsmokers, but also reduced salivary titrable base.[24]

Condensation of cigarette products injures the esophageal epithelium and makes it more susceptible to acid reflux regardless of the direct effect of lower sphincter pressure itself. Condensation products from tobacco smoke accumulate in saliva which exceed 10 times more than in blood[25]; they come into contact with epithelium and may lead to reduction in mucosal barrier function by changes in the potential difference and sign of loss of active sodium transport.[26] Due to direct effect of smoke products or indirect effect of acid by increased rate of reflux episode, there is more reactive histologic changes of epithelium in smokers.[27]

**Gastroesophageal reflux disease (GERD)**

In 1972, Stanciu and Bennett reported a 92% association between symptomatic GERD and smoking.[16] In a cross-sectional study and in a case-control study, smoking and its intensity was a risk factor for GERD[28,29]; Barrett esophagitis was also associated with smoking habit.[30] There is no cohort study on the relationship between this very common disease and nicotine abuse.

**Gastric mechanisms**

The common occurrence of peptic ulcer disease in the population, especially, among smokers, was the main research field on the acute and chronic effect of nicotine consumption on various functions of stomach, its motility, acid secretion, defense mechanisms including gastric barrier function, and morphological changes of gastric mucosa at the time, when the infectious genesis of peptic ulcer was not established.

**Gastric barrier function**

Endogenous gastric mucosal prostaglandins play an important role in the maintenance of mucosal integrity, prevent mucosal damage in animals and man,[31] stimulate gastric mucus production, and enhance gastric mucosal blood flow and nonparietal cell alkaline secretion.[32,33] Smoking reduces the synthesis of prostaglandin in the gastric mucosa and decreases the barrier function of gastric mucosa.[34]

Interleukin 8 and two other cytokines have been found to be increased in the gastric mucosa of smokers compared to nonsmokers, when they are infected with *H. pylori*. This can induce more inflammation in the gastric mucosa of smokers and enhance the progression of gastritis.[35] The concentration of vitamin C in gastric juice was

found significantly lower in smokers than nonsmokers, which was unrelated to the *H. pylori* infection in healthy persons.[36] Smoking stimulates the release of vasopressin from pituitary gland, which affects vasoconstriction toward gastric mucosa.[37, 38]

The adverse effect of cigarette smoking in the gastric mucosa includes reduction of circulating epidermal growth factor, and increase in tissue free radical production along with reduction in mucosal constitutive nitric oxide synthase activity. Furthermore, alteration in normal gastric mucosal blood flow and angiogenesis and suppression of cell proliferation contribute largely to the delay in ulcer healing in cigarette smokers.[39] Surface active phospholipids (SPL) play a key role in gastric cytoprotection. Both *H. pylori*-infected and smoker persons have higher concentrations of more polar phospholipid subclasses, which make the mucosa more vulnerable to acid attack as the gastric surfactant becomes less hydrophobic.[40]

During the hour immediately following cigarette smoking, the concentrations of bile acids, lysolecithin, and lecithin are increased by 1.6 – 2.9 folds in stomach compared to the control, which demonstrates increased duodenal reflux after smoking.[41] Increased duodenogastric reflux was observed during smoking by incompetent pylorus.[42,43] These studies may lead to loss of gastric barrier function and to damage of esophageal epithelium by reflux of gastric contents.

Iwao and coworkers measured the blood flow to the corpus and antral areas of healthy subjects by Doppler flowmetry and found an almost 30% reduction in the blood flow in both areas of stomach only during smoking.[44] This finding was confirmed in another larger study on a group of patients.[45] However, in the anesthetized rats, the reduction in blood flow in the gastric mucosa under nicotine was found to be due the general hypotension.[46] The reduction in blood flow to gastric mucosa may reduce the barrier function of the gastric mucosa. Bicarbonate secretion of gastric mucosa has been found to be reduced in smokers.[47]

**Gastric motility**

Acute cigarette smoking produces excessive antrofundal redistribution of both solid and liquid contents and delays solid and liquid gastric emptying in habitual smokers[48,49] and duodenal ulcer patients.[50] Acute smoking delays the emptying of technetium-scanned solid meal according to the concentration of serum nicotine.[51] Some authors have found that gastric emptying was only delayed by smoking which was not observed by consumption of nicotine gum.[52] Transdermal nicotine patch used in healthy nonsmoker subjects has no effect on the gastric emptying of liquid and solids.[53] On the contrary, accelerated emptying of liquid[54] and of solid[55] was reported in a small sample of healthy subjects during active smoking.

**Gastric acid secretion**

The initial maxim of Schwarz “no acid, no ulcer” governed the attention of all scientists to the gastric acid secretion as the only pathogenetic factor for the development of peptic ulcer disease for more than eight decades.[56]

The effect of acute nicotine administration on basal or stimulated acid secretion is very conflicting.[57]

In acute experiment on dogs, intravenous injection of nicotine had no effect on basal and stimulated gastric secretion as well as on the gastric blood flow and gastric barrier function on hydrogen and sodium ions, but decreased significantly the pancreatic and biliary bicarbonate secretion.[58] Sonnenberg and Husmert studied the gastric blood flow and basal gastric acid secretion under various doses of nicotine injected intravenously and found that the gastric acid volume secretion is reduced in a dose-dependent manner more intensively than gastric blood flow.[59] By injection of nicotine into the lateral cerebral ventricle, the basal acid secretion was doubled, which could be blocked by administration of atropine.[60] Chronic sham feeding in dogs increases significantly the basal acid secretion.[61] These animal experiments show that chronic smoking probably stimulates, by vagal nerve drive, the gastric acid secretion and leads to increasing parietal cell mass. In human, stimulated gastric acid secretion was further increased under different doses of intravenously injected nicotine.[62]

Whitfeld and Hobsley found that duodenal ulcer patients secrete more gastric acid than nonulcer patients.[63] It was found that smoking effect on gastric acid secretion was confined most to the men.[64]

Parente and coworkers found no change in gastric acid secretion during acute smoking in

smokers, but heavy smokers had more pentagastrin-stimulated secretion than nonsmokers.[65]

We have studied in healthy subjects the basal and pentagastrin-stimulated gastric acid secretion as well as pepsin activity in gastric juice and paid attention to the smoking habit of the subjects as well as nicotine excretion in urine of 104 men and 97 women who had no gastric lesion by endoscopy. We found that the basal and stimulated gastric acid secretion in men and only stimulated gastric acid secretion in women were significantly higher in smokers than in nonsmokers; the acid secretion was correlated with number of cigarettes smoked and duration of smoking habit.[66] This finding was confirmed later in healthy individuals and in those with peptic ulcer.[67]

**Reduced bicarbonate secretion of pancreas**

Acid gastric content is neutralized rapidly by biliary and pancreatic secretion after entering the duodenum.[68] Smoking inhibited in 25 male patients—eight of whom had duodenal ulcer—the steady basal pancreatic volume and bicarbonate secretion in all smokers and nonsmokers.[69] The degree of basal pancreatic secretion correlated well with the plasma concentration of nicotine and remains reduced up to 90 min after cessation of smoking.[68,70] Smoking inhibits secretin-stimulated pancreatic secretion in light smokers but does not affect it in heavy smokers.[71, 72] Therefore, smoking, due to its reducing effect on the pancreatic basal secretion, can lead to longer acidity in duodenum and can damage the duodenal mucosa for the colonization of *H. pylori* and development of ulcer.

**Nonulcer dyspepsia**

Nonulcer dyspepsia is a heterogeneous disease of unknown cause, which affects more than 20 – 30% of population in life-time. The most common cause of the disease is intake of nonsteroidal anti-inflammatory drugs (NSAIDs). The importance of smoking in potentiating the NSAID effect is probably present, but the results of epidemiologic studies are controversial. In one epidemiologic population-based study, the smokers with daily consumption of more than 20 cigarettes had a risk of 1.55 (CI: 1.29 – 1.86) times of nonsmokers to develop nonulcer dyspepsia.[73] In a small study, patients complained of dyspepsia, when they had *H. pylori* infection and smoking together.[74] In another population-based study, smoking, in contrary to the previous study, was an independent risk factor and not associated with *H. pylori* infection.[75] In two other case-control studies performed by the same group, smoking was not associated with nonulcer dyspepsia.[76,77] Further population-based studies are necessary for the definite answer to the role of smoking as independent factor for the high prevalence of nonulcer dyspepsia in population. Eradication therapy in smokers with nonulcer dyspepsia is less successful than in nonsmokers according to 22 published reports.[78]

**Peptic ulcer disease**

Smoking was considered in the earlier studies as an associated[79 – 81] factor in the pathogenesis of peptic ulcer disease. It has been shown that individuals affected by duodenal ulcer smoke more and start smoking at earlier age than do subjects without ulcer.[82]

From the 1979 report of National Institute of Arthritis, Metabolism, and Digestive Disease in the USA, it was a clear epidemiologic evidence that peptic ulcer patients—males and females—smoke more than the controls and that smokers of both sexes have been affected more by peptic ulcer than nonsmokers and that the prevalence of peptic ulcer is correlated with the amount of cigarettes smoked.[83]

In a large study on patients with peptic ulcer and two control populations in Norway matched for age and sex, increased risk of smoking has been found in both sexes for duodenal and gastric ulcer. The association with quantity of smoking was observed only in men with duodenal ulcer.[84]

There are many studies, which clearly show more than two-fold increase in occurrence of peptic ulcer disease among smokers. The increase of more acid secretion, the high level of serum gastrin, the lower bicarbonate secretion among smokers compared to nonsmokers have emphasized the importance of lower capacity of neutralization of acid secretion for the occurrence of peptic ulcer disease in the time when *H. pylori* infection was not known as the pivotal cause of the disease.

Smoking produces peptic ulcer disease in the duodenal bulb and stomach. The risk is associated with the number of cigarettes and the length of smoking habit.[85,86]

Continuous smoking inhibits the healing of gastric ulcer[87] and duodenal ulcer.[88–90] Smoking

became an important factor for ulcer healing and is considered by the evaluation of the efficacy of drugs.[91,92] Statistical analysis of 18 reports confirmed retardation of the healing process of duodenal and gastric ulcer under placebo and treatment with antacid and $H_2$-receptor blocking agents.[93] It has been shown that smoking diminishes the inhibitory capacity of $H_2$-receptor antagonists for enhanced healing of peptic ulcer.[94]

**Inflammatory bowel disease (IBD)**

In 1982, Harries et al found that 8% of patients with the inflammatory disease smoke compared to 44% of matched control.[95] Many epidemiologic studies revealed that the patients with ulcerative colitis may benefit from smoking, but this harms Crohn's disease.[96 – 98] Logan and coworkers found that 42 out of 55 patients with ulcerative colitis had given up the smoking eight years before the onset of the disease.[99]

Among 406 patients with IBD, 260 with ulcerative colitis, and 144 with Crohn's disease, smokers had a decreased risk of acquiring ulcerative colitis in comparison to never smokers (RR: 0.7). Smoking doubles the risk of acquiring Crohn's disease.[100] Hospitalization and surgical procedure occur most frequently in heavy smokers who quit smoking before the onset of ulcerative colitis.[101] Patients with Crohn's disease who smoke are less likely to have colonic involvement[102] and patients with ulcerative colitis who begin smoking after the diagnosis of their disease present a significant reduction in the number of recurrences.[103] Smoking is a risk factor for osteoporosis only in women with IBD.[104] It is very striking that among the Jews with IBD, the effect of smoking is not present.[105]

In a meta-analysis of 22 reports, odds ratio for association between current smoking and Chron's disease was 1.76 (95% CI: 1.40 – 2.22); for former smoking and ulcerative colitis, it was 1.79 (95% CI: 1.37 – 2.34). Current smoking had a protective effect on the development of ulcerative colitis when compared to the controls (OR: 0.58; 95% CI: 0.45 – 0.75).[106]

In patients with ulcerative colitis, the glycoprotein production in the mucosal specimen is reduced compared to the controls, but smokers among patients with ulcerative colitis had more glycoprotein in the mucosa than nonsmokers. Increased mucus production may be important for the barrier function.[107]

**Irritable bowel syndrome (IBS)**

In one study from Korea, patients with IBS were less smokers than general population (OR: 0.65),[108] but there was no association between IBS and smoking in Turkey, USA ,and Iran.[109 – 111]

**Smoking and liver**

We must be aware that the metabolism of a variety of drugs may be accelerated in smokers. Tobacco smoke induces the hepatic cytochrome P-448, which is important for metabolism of some drugs and enhances their clearance. Because of this, a lower dose of theophylline and pentazocine are needed by smokers.[112] As carboxy-hemoglobin is increased in smokers, the capacity of tissue to deliver oxygen from oxyhemoglobin due to the shift of oxygen-hemoglobin dissociation curve can be reduced and when anemia is present, hepatic tissue hypoxia may occur in critical situation. Smoking can release vasopressin[113] and norepinephrine,[114] which may contribute to sodium and water retention and worsens ascites. The role of smoking in combination with alcohol- and virus-induced benign diseases is unknown.

**Cancer in gastrointestinal tract and smoking**

About 60 chemical components in cigarette smoke are considered to be carcinogens. Nicotine seems to be a mitogenic compound in modulating tumor cell proliferation.[115]

**Oral cancer**

Oral cancer was considered to have a strong association with long use of tobacco. Up to 90% of oral cancer patients were reported to be heavy smokers.[116] Epidemiologic studies are limited to case-control studies with regard to smoking as risk factors. As the majority of smokers have poor oral hygiene, it will be very difficult to differentiate between the effect of smoking habits and poor oral hygiene on the pathogenesis of oral cancer. But in some studies, the oral hygiene and smoking both are separately evaluated. The long-term effect of smoking was stronger than poor oral hygiene for the association of smoking and oral cancer.[117] Sigmund Freud was a lover of cigar, smoked 20 cigars per day. He suffered from squamous cell carcinoma of palate over 16 years.[118] Low level of education and poor oral and dental hygiene were associated with oral cancer.[119,120] In normal buccal mucosa of heavy smokers, aneuploidy and tetraploidy were found, which regresses in those

who quitted smoking.[121] A special cancer gene (GSTM1-present genotype) was associated with heavy smoking.[122] The risk of oral cancer is less in those who smoke filtered cigarettes and is multiplicated by combined use with heavy alcohol intake.[123] In a study in Poland, the attributable risk of smoking accounted for 57% of oral cancer cases. The multiplicative effect of smoking with alcohol intake was seen in male sex in Greece[124] and in both sexes in China.[125] Smoking was not a risk factor for women in the study from Greece.[124] In most studies, the incidence of oral cancer increases with the number of cigarettes smoked.[126] In a study from Sweden, alcohol intake was a stronger risk factor than smoking.[127] In an American hospital-based study on 1009 patients with oral neoplasia and 923 age-matched controls, it was found that risk for oral cancer in association with smoking intensity was stronger in women than men.[128] The tongue was more affected than other areas in Scotland,[129] but buccal mucosa was more involved in Bangaladesh.[130]

**Cancer of esophagus**

The role of smoking and alcohol intake in the etiology of esophageal cancer is well established for a long time in many cohort studies conducted in the United States veterans,[131] British physicians,[132] and American Cancer Society volunteers (Hammond). In two large cohort studies published recently, Ishikawa and coworkers have reported the results of the development of cancer of esophagus after a follow-up time of more than 7.6 years; the risk of smoking 20 cigarettes daily compared to men who had never smoked, the pooled multivariate hazard ratio was 5.09 (95% CI: 1.80 – 14.40).[134] The effect of smoking on public health was greater than alcohol drinking in Japan. In a case-control study in China, smoking was a risk factor for any type of esophageal carcinoma in rural and urban areas.[135] In this study, the risk increased with the number of cigarettes smoked and the length of smoking. By comparison of high- and low-risk areas for esophageal cancer in Japan, a relationship between smoking intensity and cancer was found only in high-risk areas and for alcohol in low-risk areas.[136] In a 12-year follow-up study in Japan, both smoking and alcohol together were found to be risk factors; the incidence increases with the severity of consumption.[137] The amount of alcohol, but not its duration, and the duration of smoking habit, but not its intensity were associated with the incidence of squamous cell cancer of esophagus in Japan.[138] In a hospital-based case-control study conducted by International Agency for Research on Cancer (IARC, Lyon, France) in South America, for subjects exposed to smoking and alcohol, the protective effect of quitting both habits appeared to be synergistic, reaching after only five to nine years of simultaneous cessation of both exposures, a 70% risk reduction.[139] In addition to esophageal cancer, a second cancer in aerodigestive tract can occur in those heavy smokers and drinkers with family history of cancer in comparison to those with no consumption.[140] A special genotype was found to be more associated in smokers with esophageal cancer.[141] Two genotypes were found to be associated with smoking and esophageal cancer in a further study from China.[142]

**Gastric cancer (GC)**

Major causes of GC appear to be environmental rather than genetic. All cohort studies up to 1995 showed a significant increased risk of GC of the order of 1.5 – 2.5 for cigarette smokers. A meta-analysis on 40 studies suggested a risk of GC among smokers of the order of 1.5 – 1.6 as compared to nonsmokers. The summary relative risk was higher in men (1.59) than in women (1.11). In total, over 80,000 cases of GC (11% of all estimated cases) may be attributed worldwide to tobacco smoking each year.[143] In Japan, the country with higher prevalence of GC, up to the end of 2006, ten cohort and 16 case-control studies were identified. In men, most studies reported moderate to strong positive associations between smoking and GC. The summary relative risk for current smokers was estimated to be 1.56 for total population (95% CI: 1.36 – 1.80)—1.79 for men (95% CI: 1.51 – 2.12), and 1.22 (1.07 – 1.38) for women.[144] In a cohort study, among the Norwegian population, the independent dose-response relation was found with earlier age at start of smoking, frequency, and duration of smoking. The risk was almost twice as high in daily smokers compared to never smokers. Combined with alcohol intake in heavy smokers, the risk of noncardia cancer was nearly five folds higher compared to nonusers.[145] In a cohort study from 10 European countries with a population more than half a million over at least four years, the association of GC and diet as well as with smoking was studied. The hazard ratio for cardia GC adjusted for education, fresh fruit

intake, and body mass index, was 4.1; for distal GC it was 1.94. In this cohort study, 17.6% of GC cases may be attributable to smoking habit (OR 10; 95% CI: 5 – 29). Significant decrease of hazard ratio was observed, when the subject quitted smoking more than 10 years.[146] By a follow-up study of almost 20,000 subjects over 10 years, association of smoking habit was observed with the differentiated type of distal GC.[147] This association of smoking with differentiated type among 995 GC cases was confirmed in a further study from Japan where it was more stronger in younger age group than in the older one.[148] In one case-control study from Russia, there was no association between smoking and GC in those who drink Vodka;[149] in another case-control study from Russia, it was an association between smoking and GC only in men but not in women.[150] Survival of 877 patients with GC was associated with smoking habit in a prospective study over six years.[151]

**Smoking and colon and rectal cancer**

From a long follow-up study on death cause in British doctors and US veterans, the risk of smoking for development of colon cancer is present, but its effect is very small.[131,132] In a case-control study conducted in the USA, it was found that some genotypes of GSTT1 and GSTM1 among smokers have smaller risk for colon cancer.[152] Earlier studies have shown that smokers were found to have an advanced stage of cancer than did nonsmokers.[153,154] In another study, advanced stage was found only in women smokers, but smokers of both sexes had a lower mean age at diagnosis of colon and rectal cancer.[155] In a hospital-based study in Japan, no relationship was found between smoking habit and colon cancer, but there was a correlation with rectal cancer.[156] In a large case-control study in the USA, only heavy smokers with a daily consumption of more than a pack per day had 40% increased risk for colon cancer.[157] The same authors reported that individuals with genotype CYP1A1 had risk for developing colon cancer.[158] The advanced stage of colon and rectal cancer and development of cancer in earlier ages in smokers show that smoking modifies the host immune defense against tumor.

**Pancreas cancer and smoking**

In two cohort studies from 1963 and 1975 with a follow-up of more than 15 years, active smokers had a two-fold risk for pancreatic cancer,[131,132] but household passive smokers had no risk for tumor.[159] In a Swedish cohort study of more than 80,000 men and women, followed over five to ten years, current smokers had a five-fold risk compared to never smokers.[160]

In a hospital-based case-control study from Italy, smoking is a risk factor for pancreas cancer (OR=2.36; 95% CI: 1.53 – 3.63). After cessation of smoking for 15 years, the risk will be dropped to the risk of life-time nonsmokers.[161] In a cohort study of 110,792 inhabitants of a city in Japan with a follow-up of more than seven years, the relative risks of smoking for the development of pancreatic cancer was 1.6 (95% CI: 0.95 – 2.6) in men, and 1.7 (95% CI: 0.84 – 3.3) in women. Men who smoked more than 40 cigarettes per day had a substantially higher risk of pancreatic cancer with a relative risk of 3.3 (95% CI: 1.4 – 8.1). A decreasing trend was seen after cessation of smoking.[162] In a further cohort study in the USA, the proportion of pancreatic cancer attributable to smoking was 25%.[163]

In all other cohort[164] or case-control studies, the risk of smoking with various intensities could be confirmed.[165–167] In a theoretical scenario, if all smokers in Europe begin to quit smoking, there would be a reduction of pancreatic cancer up to the year 2015 of about 45% and 30% for men and women, respectively.[168] It is believed that smoking is responsible for up to 30% of pancreatic cancer and the gene CYP 1A1 and polymorphism of P53 can be affected by smoking which enhance pancreas carcinoma.[169]

**Smoking and hepatocellular carcinoma (HCC)**

The risk factors for the development of HCC are well studied by cohort and case-control studies in Japan, where this tumor has the highest incidence in the world. Beside alcohol and hepatitis B and C infection, attention was paid to smoking habits.

In a large-scale cohort study starting in 1966, up to 1982, with a 1.7-million person-years follow-up, 123 subjects developed liver cancer. The relative risk to develop liver cancer was 3.09 (95% CI: 1.78 – 5.35) for those smoked less than 30 and 6.83 (95% CI: 3.56 – 13.10) for those smoked more than 30 cigarettes per day.[170] In a meta-analysis performed in Japan, nine out of 12 cohort studies and five of 11 case-control studies found an association between smoking and liver cancer. A dose-response relationship between smoking and

liver cancer was found in three cohort and in one case-control studies.[171] Among 250,000 US veterans from first World War, the relative risk for liver cancer was 2.4 (95% CI: 1.6 – 3.5).[172] In a study from Korea among a population of more than one million, 3,807 died from liver cancer. Current male smokers but not women had a relative risk of 1.4 (95% CI: 1.3 – 1.6) for liver cancer.[173] In many other studies from the USA,[174,175] Taiwan,[176,177] Greece,[178,179] and Hong Kong[180] a positive association between smoking and liver cancer was confirmed in some with a dose-response effect.[174,178] In one case-control study, smoking was alone an important risk factor (OR=4.9; 95% CI: 2.2 – 10.6) and had with alcohol and obesity combined, a synergistic effect on development of liver cancer.[181] In few other studies, no clear relationship was found between smoking and HCC.[182 – 184] In one study, smoking could increase the incidence of liver cancer among alcohol abusers.[185]

In conclusion, among environmental factors affecting the length of our life and the longevity of humans, besides inappropriate nutrition, lack of adequate body exercise, alcohol intake, work stress ,and air pollution, smoking plays an important and probably a central role. Its significant effect arises from the widespread use among one-third of population and more importantly from silent and slow development of various diseases over many decades not noticed by the affected subject. The mechanism of the effects of smoking is very different in GI tract. The release of many mediators from nerve system and endocrine organs has stimulatory or inhibitory effect on the function of organs. Nicotine can interact with genes and induce cell alteration. Some gene polymorphisms might be more sensitive to the effects of nicotine and might enhance cell proliferation and carcino-genesis. The awareness of the physicians and thereby the population is focused mostly on the hazardous effects of nicotine on cardiovascular, cerebral, and bronchial organs. The involvement of smoking in the pathogenesis of GI diseases merits consideration for giving the adequate information to the population and intense recommendation for its cessation. Long-term cohort studies are needed to confirm the effects of smoking cessation on GI diseases.

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## References

**1** Brunton LL, Gilman A, Brunton LL, Lazo JS, Parker KL. *Goodman and Gilman, the Pharmacological Basis of Therapeutic*. 11 ed. New York: McGraw-Hill. 2006: 217 – 236.

**2** Di Chara G. Behavioral pharmacology and neurobiology of nicotine reward and dependence. In: Clementi F, Fornasari D, Gotti C, eds. *Neuronal Nicotine Receptors*. Berlin: Springer Verlag; 2000: 603 – 750.

**3** Holt PG. Immune and inflammatory function in cigarette smokers. *Thorax*. 1987; **42:** 241 – 249.

**4** Narkiewicz K, van de Borne PJ, Hausberg M, Cooley RL, Winniford MD, Davison DE, et al. Cigarette smoking increases sympathetic outflow in humans. *Circulation*. 1998; **98:** 528 – 534.

**5** Rietbrock N, Kunkel S, Wörner W, Eyer P. Oxygen-dissociation kinetics in the blood of smokers and non-smokers: interaction between oxygen and carbon monoxide at the hemoglobin molecule. *Naunyn Schmiedebergs Arch Pharmacol*. 1992; **345:** 123 – 128.

**6** Ryter SW, Otterbein LE. Carbon monoxide in biology and medicine. Bioessays. 2004; **26:** 270 – 280.

**7** Neunteufl T, Heher S, Kostner K, Mitulovic G, Lehr S, Khoschsorur G, et al. Contribution of nicotine to acute endothelial dysfunction in long-term smokers. *J Am Coll Cardiol*. 2002; **39:** 251 – 256.

**8** Morrow JD, Frei B, Longmire AW, Gaziano JM, Lynch SM, Shyr Y, et al. Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers. Smoking as a cause of oxidative damage. *N Engl J Med*. 1995; **332:** 1198 – 1203.

**9** Taybos G. Oral changes associated with tobacco use. *Am J Med Sci*. 2003; **326:** 179 – 182.

**10** Pindborg JJ. Tobacco and gingivitis. *J Dent Res*. 1947; **26:** 261 – 265.

**11** Brandtzaeg P, Jamison HC. A study of periodontal health and oral hygiene in Norwegian army recruits. *J Periodotol*. 1964; **35:** 302 – 306.

**12** Duncan HF, Pitt- Ford TR. The potential association between smoking and endodontic disease. *Int Endod J*. 2006; **39:** 843 – 854.

**13** Shizukuishi S. Smoking and periodontal disease. *Clin Calcium*. 2007; **17:** 226 – 232.

**14** Bastiaan RJ, Waite IM. Effects of tobacco smoking on plaque development and gingivitis. *J Periodontol*. 1978; **49:** 480 – 482.

**15** Dennish GW, Castell DO. Inhibitory effect of smoking on the lower esophageal sphincter. *N Engl J Med*. 1971; **284:** 1136 – 1137.

**16** Stanciu C, Bennett JR. Smoking and gastroesophageal reflux. *Brit Med J*. 1972; **3:** 793 – 795.

**17** Chattopadhay DK, Greaney ML, Irvin TT. Effect of smoking on the lower esophageal sphincter. *Gut*. 1977; **18:** 833 – 835.

**18** Rattan S, Goyal- Smit CF, Copper MP, van Leeuwen JA, Schoots IG, Stanojcic LD. Effect of cigarette smoking on gastropharyngeal and gastroesophageal reflux. *Ann Otol Rhinol Laryngol*. 2001; **110:** 190 – 193.

**19** Kahrilas PJ, Gupta RR. Mechanisms of acid reflux associated with cigarette smoking. *Gut*. 1990; **31:** 4 – 10.

**20** Kahrilas PJ. Cigarette smoking and gastroesophageal reflux disease. *Dig Dis*. 1992; **10:** 61 – 71.

**21** Kadakia SC, Kikendall JW, Maydonovitch C, Johnson

LF. Effect of cigarette smoking on gastroesophageal reflux measured by 24-h ambulatory esophageal pH monitoring. *Am J Gastroenterol*. 1995; **90:** 1785 – 1790.
**22** Smit CF, Copper MP, van Leeuwen JA, Schoots IG, Stanojcic LD. Effect of cigarette smoking on gastropharyngeal and gastroesophageal reflux. *Ann Otol Rhinol Laryngol*. 2001; **110:** 190 – 193.
**23** Kjellin G, Tibbling L. Influence of body position, dry and water swallows, smoking, and alcoholon esophageal acid clearing. Scand. *J Gastroenterol*. 1978; **13:** 283 – 288.
**24** Kahrilas PJ, Gupta PR. The effect of cigarette smoking on salivation and esophageal acid clearance. *J Lab Clin Med*. 1989; **114:** 431 – 438.
**25** Feyerabend C, Higebottam T, Russel MAH. Nicotine concentrations in urine and saliva of smokers and nonsmokers. *Brit Med J*. 1982; **284:** 1002 – 1004.
**26** Orlando RC, Powel DW, Bryson JC, Rumbaugh MM. Extreact of cigarette smoke alters esophageal mucosal function in the rabbit. *Gastroenterology*. 1982; **82:** 1141 – 1144.
**27** Auerbach O, Stout AP, Hammond EC, Garfinkel I. Histologic changes in esophagus in relation to smoking habits. *Arch Environ Health*. 1965; **11:** 4 – 15.
**28** Watanabe Y, Fujiwara Y, Shiba M, Watanabe T, Tominaga K, Oshitani N, et al. Cigarette smoking and alcohol consumption associated with gastro-oesophageal reflux disease in Japanese men. *Scand J Gastroenterol*. 2003; **38:** 807 – 811.
**29** Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Lifestyle- related risk factors in the aetiology of gastro-oesophageal reflux. *Gut*. 2004; **53:** 1730 – 1735.
**30** Smith KJ, O'Brien SM, Smithers BM, Gotley DC, Webb PM, Green AC,et al.. Interactions among smoking, obesity, and symptoms of acid reflux in Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev*. 2005; **14:** 2481 – 2486.
**31** McCready DR, Clark L, Cohen MM. Cigarette smoking reduces human gastric luminal prostaglandin E2. *Gut*. 1985; **26:** 1192 – 1196.
**32** Miller TA. Protective effects of prostaglandins against gastric mucosal damage: current knowledge and proposed mechanisms. *Am J Physiol*. 1983; **245:** G601 – G623.
**33** Robert A. Cytoprotection by prostaglandins. *Gastroenterology*. 1979; **77:** 761 – 767.
**34** Quimby GF, Bonnice CA, Burstein SH, Eastwood GL. Active smoking depresses prostaglandin synthesis in human gastric mucosa. *Ann Intern Med*. 1986; **104:** 616 – 619.
**35** Shimoyama T, Everett SM, Fukuda S, Axon AT, Dixon MF, Crabtree JE. Influence of smoking and alcohol on gastric chemokine mRNA expression in patients with *Helicobacter pylori* infection. *J Clin Pathol*. 2001; **54:** 332 – 334.
**36** Jarosz M, Dzieniszewski J, Dabrowska-Ufniarz E, Wartanowicz M, Ziemlanski S. Tobacco smoking and vitamin C concentration in gastric juice in healthy subjects and patients with *Helicobacter pylori* infection. *Eur J Cancer Prev*. 2000; **9:** 423 – 428.
**37** Rowe JW, Kilgore A, Robertson GL. Evidence in man that cigarette smoking induces vasopressin release via airway-specific mechanism. *J Clin Endocrinol Metab*. 1980; **51:** 170 – 172.
**38** Ritchie WJ jr. Acute gastric mucosal damage induced by bile salts, acid, and ischemia. *Gastroenterology*. 1975; **68:** 699 – 707.
**39** Ko JK, Cho CH. Alcohol drinking and cigarette smoking: a "partner" for gastric ulceration. *Zhonghua Yi Xue Za Zhi (Taipei)*. 2000; **63:** 845 – 854.
**40** Wenner J, Gunnarsson T, Graffner H, Lindell G. Influence of smoking and *Helicobacter pylori* on gastric phospholipids. *Dig Dis Sci*. 2000; **45:** 1648 – 1652.
**41** Begemann F, Schwoy M, Schumperlick V. Zigarettenrauchen und duodenogastric reflux [in Germany]. *Innere Medizin*. 1980; **7:** 165 – 168.
**42** Valenzuela JE, Defilippi C, Csendes A. Manometric studies on the human pyloric sphincter. Effect of cigarette smoking, metoclopramide, and atropine. *Gastroenterology*. 1976; **70:** 481 – 483.
**43** Read NW, Grech P. Effect of cigarette smoking on competence of the pylorus, preliminary study. *Brit Med J*. 1973; **3:** 313 – 316.
**44** Iwao T, Toyonaga A, Ikegami M, Oho K, Sumino M, Sakaki M, et al. Gastric mucosal blood flow after smoking in healthy human beings assessed by laser Doppler flowmetry. *Gastrointest Endosc*. 1993; **39:** 400 – 403.
**45** Taha AS, Angerson W, Nakshabendi I, Beekman H, Morran C, Sturrock RD, et al. Gastric and duodenal mucosal blood flow in patients receiving nonsteroidal anti-inflammatory drugs—influence of age, smoking, ulceration, and *Helicobacter pylori*. *Aliment Pharmacol Ther*. 1993; **7:** 41 – 45.
**46** Robert ME, Leung FW, Guth PH. Nicotine and smoking do not decrease basal gastric mucosal blood flow in anesthetized rats. *Dig Dis Sci*. 1986; **31:** 530 – 534.
**47** Dal- Santo P, Vianello F, Germana B, Del- Bianco T, Laino G, Grassi SA, et al. Gastric bicarbonate secretion in high-relapsing, smoking duodenal ulcer patients. *Hepatogastroenterology*. 1993; **40:** 120 – 122.
**48** Scott AM, Kellow JE, Shuter B, Nolan JM, Hoschl R, Jones MP. Effects of cigarette smoking on solid and liquid intragastric distribution and gastric emptying. *Gastroenterology*. 1993; **104:** 410 – 416.
**49** Johnson RD, Horowitz M, Maddox AF, Wishart JM, Shearman DJ. Cigarette smoking and rate of gastric emptying: effect on alcohol absorption. *BMJ*. 1991; **302:** 20 – 23.
**50** Nowak A, Jonderko K, Kaczor R, Nowak S, Adamczak D, Rudzki K. Inhibitory effect of cigarette smoking on gastric emptying of a solid meal in patients with type I gastric ulcer. *Z Gastroenterol*. 1991; **29:** 45 – 48.
**51** Gritz ER, Ippoliti A, Jarvik ME, Rose JE, Shiffman S, Harrison A, et al. The effect of nicotine on the delay of gastric emptying. *Aliment Pharmacol Ther*. 1988; **2:** 173 – 178.
**52** Miller G, Palmer KR, Smith B, Ferrington C, Merrick MV. Smoking delays gastric emptying of solids. *Gut*. 1989; **30:** 50 – 53.
**53** Wong PW, Kadakia SC, McBiles M. Acute effect of nicotine patch on gastric emptying of liquid and solid contents in healthy subjects. *Dig Dis Sci*. 1999; **44:** 2165 – 2171.
**54** Grimes DS, Goddard J. Effect of cigarette smoking on gastric emptying. *Br Med J*. 1978; **2:** 460 – 461.
**55** Sanaka M, Anjiki H, Tsutsumi H, Abe K, Kawakami T, Saitoh M, et al. Effect of cigarette smoking on gastric emptying of solids in Japanese smokers: a crossover

study using the 13C-octanoic acid breath test. *J Gastroenterol*. 2005; **40:** 578 – 582.
**56** Schwarz K. Über penetrierende Magen- und Jejunalgeschwüre [in Germany]. *Beitr Klin Chir*. 1910; **67:** 96 – 128.
**57** Endoh K, Leung FW. Effects of smoking and nicotine on the gastric mucosa: a review of clinical and experimental evidence. *Gastroenterology*. 1994; **107:** 864 – 878.
**58** Konturek SJ, Solomon TE, McCreight WG, Johnson LR, Jacobson ED. Effect of nicotine on gastrointestinal secretion. *Gastroenterology*. 1971; **60:** 1098 – 1105.
**59** Sonnenberg A, Husmert N. Effect of nicotine on gastric mucosal blood flow and acid secretion. *Gut*. 1982; **23:** 532 – 559.
**60** Osumi Y, Ishikawa T, Nagasaka Y, Fujiwara M. Central effect of on gastric acid secretion in rats. *Eur J Pharamacol*. 1980; **68:** 409 – 415.
**61** Thirlby RC, Feldman M. Effect of chronic sham feeding on maximal gastric acid secretion in the dog. *J Clin Invest*. 1984; **73:** 566 – 569.
**62** Mertz DP, Thongbhoubesra T. Effect of nicotine on the production of gastric acid. *Med Klin*. 1976; **71:** 147 – 155.
**63** Whitfeld PF, Hobsley M. Maximal gastric secretion in smokers and nonsmokers with duodenal ulcer. *Brit. J Surg*. 1985; **72:** 955 – 957.
**64** Whitfield PF, Hobley M. Comparison of maximal gastric secretion in smokers and non-smokers with and without duodenal ulcer. *Gut.* 1987; **28:** 557 – 560.
**65** Parente F, Lazzaroni M, Sangaletti O, Baroni S, Bianchi-Porro G. Cigarette smoking, gastric acid secretion, and serum pepsinogen I concentrations in duodenal ulcer patients. *Gut*. 1985; **26:** 1327 – 1332.
**66** Massarrat S, Enschai F, Pittner PM. Increased gastric secretory capacity in smokers without gastrointestinal lesions. *Gut.* 1986; **27:** 433 – 439.
**67** Lanas A, Hirschowity BI. Influence of smoking on basal and on vagally and maximally stimulated gastric acid and pepsin secretion. *Scand J Gastroenterol*. 1992; **27:** 208 – 212.
**68** Murthy SNS, Dinosi VP Jr, Clearfield HR, Chey WJ. Simultaneous measurement of basal pancreatic, gastric acid secretion, plasma gastrin, and secretin during smoking. *Gastroenterology*. 1977; **73:** 754 – 764.
**69** Bochenek WJ, Koronczewski R. Effect of cigarette smoking on bicarbonate and volume of duodenal contents. *Am J Dig Dis*. 1973; **18:** 729 – 733.
**70** Murthy SNS, Dinosi VP Jr, Clearfield HR, Chey WJ. Serial pH changes in the duodenal bulb during smoking. *Gastroenterology*. 1978; **75:** 1 – 4.
**71** Bynum TE, Solomon TE, Johnson LR, Jacobson ED. Inhibition of pancreatic secretion in man by cigarette smoking. *Gut*. 1972; **13:** 361 – 365.
**72** Brown P. Influence of smoking on pancreatic function in man. *Med J Aust*. 1976; **2:** 290 – 293.
**73** Ristensen M, Hansen JM, De Muckadell OB. Risk factors for dyspepsia in a general population: nonsteroidal anti-inflammatory drugs, cigarette smoking, and unemployment are more important than *Helicobacter pylori* infection. *Scand J Gastroenterol*. 2006; **41:** 149 – 154.
**74** Halter F, Brignoli R. *Helicobacter pylori* and smoking: two additive risk factors for organic dyspepsia. *Yale J Biol Med*. 1998; **71:** 91 – 99.
**75** Nandurkar S, Talley NJ, Xia H, Mitchell H, Hazel S, Jones M. Dyspepsia in the community is linked to smoking and aspirin use but not to *Helicobacter pylori* infection. *Arch Intern Med*. 1998; **158:** 1427 – 1433.
**76** Talley NJ, McNeil D, Piper DW. Environmental factors and chronic unexplained dyspepsia. Association with acetaminophen but not other analgesics, alcohol, coffee, tea, or smoking. *Dig Dis Sci*. 1988; **33:** 641 – 648.
**77** Talley NJ, Weaver AL, Zinsmeister AR. Smoking, alcohol, and nonsteroidal anti-inflammatory drugs in outpatients with functional dyspepsia and among dyspepsia subgroups. *Am J Gastroenterol*. 1994; **89:** 524 – 528.
**78** Suzuki T, Matsuo K, Ito H, Sawaki A, Hirose K, Wakai K, et al. Smoking increases the treatment failure for *Helicobacter pylori* eradication. *Am J Med*. 2006; **119:** 217 – 224.
**79** Jedrychowsky W, Popiela T. Association between the occurrence of peptic ulcers and tobacco smoking. *Public Health*. 1974; **88:** 195 – 200.
**80** Friedman GD, Sieglab AB, Seltzer CC. Cigarettes, alcohol, coffee, and peptic ulcer. *N Engl J Med*. 1974; **290:** 469 – 473.
**81** Gillies MA, Skyring A. Gastric and duodenal ulcer. The association between aspirin ingestion, smoking, and family history of ulcer. *Med J Aust*. 1969; **2:** 280 – 285.
**82** Monson RR. Cigarette smoking and body form in peptic ulcer. *Gastroenterology*. 1970; **58:** 337 – 344.
**83** Smoking and Health, a report of the Surgeon General. United States Department of Health, Education, and Welfare; 1979: 1 – 21.
**84** Ostensen H, Gudmundsen TE, Ostensen M, Burhol PG, Bonnevie O. Smoking, alcohol, coffee, and familial factors: any associations with peptic ulcer disease? A clinically and radiologically prospective study. *Scand J Gastroenterol*. 1985; **20:** 1227 – 1235.
**85** Kato I, Nomura AM, Stemmermann GN, Chyou PH. A prospective study of gastric and duodenal ulcer and its relation to smoking, alcohol, and diet. *Am J Epidemiol*. 1992; **135:** 521 – 530.
**86** Piper DW, McIntosh JH, Greig M, Shy CM. Environmental factors and chronic gastric ulcer. A case-control study of the association of smoking, alcohol, and heavy analgesic ingestion with the exacerbation of chronic gastric ulcer. *Scand J Gastroenterol*. 1982; **17:** 721 – 729.
**87** Doll R, Jones FA, Pygott F. Effect of smoking on the production and maintenance of gastric and duodenal ulcers. *Lancet.* 1958; **I:** 657 – 662.
**88** Massarrat S, Eisenmann A. Factors affecting the healing rate of duodenal and pyloric ulcer with low- dose antacid treatment. Gut. 1981; **22:** 97 – 102.
**89** Massarrat S, Muller HG, Schmitz-Moormann P. Risk factors for healing of duodenal ulcer under antacid treatment: do ulcer patients need individual treatment? *Gut*. 1988; **29:** 291 – 297.
**90** Sonnenberg A, Müller-Lissner SA, Vogel E, Schmid P, Gonvers JJ, Peter P, et al. Predictors of duodenal ulcer healing and relapse. *Gastroenterology.* 1981; **81:** 1061 – 1067.
**91** Korman MG, Hanski J, Merrett AC, Schmitd GT. Ranitidine in duodenal ulcer, incidence of healing, and effect of smoking. *Dig Dis Sci*. 1982; **27:** 712 – 715.
**92** Korman MG, Hansky J, Eaves ER, Schmidt GT.

Influence of cigarette smoking on healing and relapse in duodenal ulcer disease. *Gastroenterology*. 1983; **85:** 871 – 874 .
**93** Boyd EJS, Wilson JA, Wormsley KG. Smoking impairs therapeutic gastric inhibition. *Lancet.* 1983, **I:** 95 – 97.
**94** Kikendall JW, Evaul J, Johnson LF. Effect of cigarette smoking on gastrointestinal physiology and non-neoplastic digestive disease. *J Clin Gasteroenterol*. 1984; **6:** 65 – 78.
**95** Harries AD, Baird A, Rhodes J. Nonsmoking, a feature of ulcerative colitis. *Br Med J*. 1982; **284:** 706.
**96** Bures J, Fixa B, Komarkova O, Fingerland A. Nonsmoking, a fieature of ulcerative colitis. *Br Med J*. 1982; 285: 440.
**97** Jick H, Walker AM. Cigarette smoking and ulcerative colitis. *N Engl J Med*. 1983; **308:** 261 – 263.
**98** Bailar JC 3rd. Cigarette, ulcerative colitis, and inference from uncontrolled data. *N Engl J Med*. 1983; **308:** 275 – 277.
**99** Logan RFA, Edmond M, Sommerwille KW, Lngman MJS. Smoking and ulcerative colitis. *Br Med J*. 1984; **288:** 751 – 753.
**100** Lindberg E, Tysk C, Andersson K, Järnerot G. Smoking and inflammatory bowel disease. A case- control study. Gut. 1988; **29:** 352 – 357.
**101** Boyko EJ, Perera DR, Koepsell TD, Keane EM, Inui TS. Effect of cigarette smoking on the clinical course of ulcerative colitis. *Scand J Gastroenterol*. 1988; **23:** 1147 – 1152.
**102** Russel MG, Volovics A, Schoon EJ, van Wijlick EH, Logan RF, Shivananda S, et al. Inflammatory bowel disease: is there any relation between smoking status and disease presentation? European Collaborative IBD Study Group. *Gastroenterology*. 1995; **108:** 1683 – 1687.
**103** Fraga XF, Vergara M, Medina C, Casellas F, Bermejo B, Malagelada JR. Effects of smoking on the presentation and clinical course of inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 1997; **9:** 683 – 687.
**104** Silvennoinen JA, Lehtola JK, Niemela SE. Smoking is a risk factor for osteoporosis in women with inflammatory bowel disease. *Scand J Gastroenterol*. 1996; **31:** 367 – 371.
**105** Reif S, Klein I, Arber N, Gilat T. Lack of association between smoking and inflammatory bowel disease in Jewish patients in Israel. *Inflamm Bowel Dis*. 1998; **4:** 182 – 186.
**106** Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc*. 2006; **81:** 1462 – 1471.
**107** Cope GF, Heatley RV, Kelleher JK. Smoking and colonic mucus in ulcerative colitis. *Br Med J (Clin Res Ed)*. 1986; **293:** 481.
**108** Han SH, Lee OY, Bae SC, Lee SH, Chang YK, Yang SY, et al. Prevalence of irritable bowel syndrome in Korea: population-based survey using the Rome II criteria. *J Gastroenterol Hepatol*. 2006; **21:** 1687 – 1692.
**109** Karaman N, Turkay C, Yonem O. Irritable bowel syndrome prevalence in city center of Sivas. *Turk J Gastroenterol*. 2003; **14:** 128 – 131.
**110** Locke GR 3rd, Zinsmeister AR, Talley NJ, Fett SL, Melton LJ. Risk factors for irritable bowel syndrome: role of analgesics and food sensitivities. *Am J Gastroenterol*. 2000; **95:** 157 –1 65.
**111** Massarrat S, Saberi-Firoozi M, Soleimani A, Himmelmann GW, Hitzges M, Keshavarz H. Peptic ulcer disease, irritable bowel syndrome, and constipation in two populations in Iran. *Eur J Gastroenterol Hepatol*. 1995; **7:** 427 – 433.
**112** Dawson GW, Vestal RE. Smoking and drug metabolism. *Pharmacol Ther*. 1982; **15:** 221.
**113** Husain MK, Franty AG, Ciarochi F, Robinson AG. Nicotine-stimulated release of neurophysin and vasopressin in humans. *J Clin Endocrinol Metabol*. 1975; **41:** 1113 – 1117.
**114** Cyrer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. *N Engl J Med*. 1976; 295: 573 – 577.
**115** Shin VY, Cho CH. Nicotine and gastric cancer. *Alcohol*. 2005; **35b:** 259 – 264.
**116** Lumukana R, King T. Smoking and chewing habits of oral cancer patients in the Solomon Islands. *Pac Health Dialog*. 2003; **10:** 41 – 44.
**117** Marshall JR, Graham S, Haughey BP, Shedd D, O'Shea R, Brasure J, et al. Smoking, alcohol, dentition, and diet in the epidemiology of oral cancer. *Eur J Cancer B Oral Oncol*. 1992; **28B:** 9 – 15.
**118** Adeyemo WL. Sigmund Freud: smoking habit, oral cancer, and euthanasia. *Niger J Med*. 2004; **13:** 189 – 195.
**119** Guneri P, Cankaya H, Yavuzer A, Guneri EA, Erisen L, Ozkul D, et al. Primary oral cancer in a Turkish population sample: association with sociodemographic features, smoking, alcohol, diet, and dentition. *Oral Oncol*. 2005; **41:** 1005 – 1012.
**120** Balaram P, Sridhar H, Rajkumar T, Vaccarella S, Herrero R, Nandakumar A, et al. Oral cancer in southern India: the influence of smoking, drinking, paan-chewing, and oral hygiene. *Int J Cancer*. 2002; **98:** 440 – 445.
**121** Sudbo J, Samuelsson R, Risberg B, Heistein S, Nyhus C, Samuelsson M, et al. Risk markers of oral cancer in clinically normal mucosa as an aid in smoking cessation counseling. *J Clin Oncol*. 2006; **24:** 2404.
**122** Xie H, Hou L, Shields PG, Winn DM, Gridley G, Bravo-Otero E, et al. Metabolic polymorphisms, smoking, and oral cancer in Puerto Rico. *Oncol Res*. 2004; **14:** 315 – 320.
**123** Lissowska J, Pilarska A, Pilarski P, Samolczyk-Wanyura D, Piekarczyk J, Bardin-Mikollajczak A, et al. Smoking, alcohol, diet, dentition, and sexual practices in the epidemiology of oral cancer in Poland. *Eur J Cancer Prev*. 2003; **12:** 25 – 33.
**124** Zavras AI, Douglass CW, Joshipura K, Wu T, Laskaris G, Petridou E, et al. Smoking and alcohol in the etiology of oral cancer: gender-specific risk profiles in the south of Greece. *Oral Oncol*. 2001; **37:** 28 – 35.
**125** Zheng TZ, Boyle P, Hu HF, Duan J, Jiang PJ, Ma DQ, et al. Tobacco smoking, alcohol consumption, and risk of oral cancer: a case-control study in Beijing, People's Republic of China. *Cancer Causes Control*. 1990; **1:** 173 – 179.
**126** Moreno-Lopez LA, Esparza-Gomez GC, Gonzalez-Navarro A, Cerero-Lapiedra R, Gonzalez-Hernandez MJ, Dominguez-Rojas V. Risk of oral cancer associated with tobacco smoking, alcohol consumption, and oral hygiene: a case-control study in Madrid, Spain. *Oral Oncol*. 2000; **36:** 170 – 174.
**127** Schildt EB, Eriksson M, Hardell L, Magnuson A. Oral

snuff, smoking habits, and alcohol consumption in relation to oral cancer in a Swedish case-control study. *Cancer Res*. 1996; **56:** 5192 – 5197.
**128** Muscat JE, Richie JP Jr, Thompson S, Wynder EL. Gender differences in smoking and risk for oral cancer. *Int J Cancer*. 1998; **77:** 341 – 346.
**129** Llewelyn J, Mitchell R. Smoking, alcohol, and oral cancer in south-east Scotland: a 10-year experience. *Br J Oral Maxillofac Surg*. 1994; **32:** 146 – 152.
**130** Ahmed F, Islam KM. Site predilection of oral cancer and its correlation with chewing and smoking habit, a study of 103 cases. *Bangladesh Med Res Counc Bull*. 1990; **16:** 17 – 25.
**131** Rogot E, Murray JL. Smoking and cause of death among U.S. veterans: 16 years of observation. *Public Health Rep*. 1980: **95:** 213 – 222.
**132** Doll R, Peto R. Mortality in relation to smoking: 20 years' observation on male British doctors. *Br Med J*. 1976: 2: 1525 – 1536.
**133** Hammond EC. Smoking in relation to the death rates of one-million men and women. Natl Cancer Inst Monogr. 1966; 19: 127 – 204.
**134** Ishikawa A, Kuriyama S, Tsubono Y, Fukao A, Takahashi H, Tachiya H, et al. Smoking, alcohol drinking, green tea consumption, and the risk of esophageal cancer in Japanese men. *J Epidemiol*. 2006; **16:** 185 – 192.
**135** Jiang JM, Zeng XJ, Chen JS, Ping-zhao, Li JY, Zhang KL, et al. Smoking and mortality from esophageal cancer in China: a large case-control study of 19,734 male esophageal cancer deaths and 104,846 living spouse controls. *Int J Cancer*. 2006; **119:** 1427 – 1432.
**136** Wu M, Zhao JK, Hu XS, Wang PH, Qin Y, Lu YC, et al. Association of smoking, alcohol drinking,and dietary factors with esophageal cancer in high- and low-risk areas of Jiangsu Province, China. *World J Gastroenterol*. 2006; **12:** 1686 – 1693.
**137** Sakata K, Hoshiyama Y, Morioka S, Hashimoto T, Takeshita T, Tamakoshi A. JAAC Study Group. Smoking, alcohol drinking, and esophageal cancer: findings from the JAAC Study. *J Epidemiol*. 2005; **15 (suppl 2):** S212 – S219.
**138** Lee CH, Lee JM, Wu DC, Hsu HK, Kao EL, Huang HL, et al. Independent and combined effects of alcohol intake, tobacco smoking, and betel quid chewing on the risk of esophageal cancer in Taiwan. *Int J Cancer*. 2005; **113:** 475 – 482.
**139** Castellsague X, Munoz N, De Stefani E, Victora CG, Quintana MJ, Castelletto R, et al. Smoking and drinking cessation and risk of esophageal cancer (Spain). *Cancer Causes Control*. 2000; **11:** 813 – 818.
**140** Morita M, Kuwano H, Ohno S, Sugimachi K, Seo Y, Tomoda H, et al. Multiple occurrence of carcinoma in the upper aerodigestive tract associated with esophageal cancer: reference to smoking, drinking, and family history. *Int J Cancer*. 1994; **58:** 207 – 210.
**141** Yu HP, Zhang XY, Wang XL, Shi LY, Li YY, Li F, et al. DNA repair gene XRCC1 polymorphisms, smoking, and esophageal cancer risk. *Cancer Detect Prev*. 2004; **28:** 194 – 199.
**142** Wang AH, Sun CS, Li LS, Huang JY, Chen QS. Relationship of tobacco smoking CYP1A1 GSTM1 gene polymorphism and esophageal cancer in Xi'an. *World J Gastroenterol*. 2002; **8:** 49 – 53.
**143** Tredaniel J, Boffetta P, Buiatti E, Saracci R, Hirsch A. Tobacco smoking and gastric cancer: review and meta-analysis. *Int J Cancer*. 1997; **72:** 565 – 573.
**144** Nishino Y, Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, et al. Tobacco smoking and gastric cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol*. 2006; **36:** 800 – 807.
**145** Sjödahl K, Lu Y, Nilsen TI, Ye W, Hveem K, Vatten L, et al. Smoking and alcohol drinking in relation to risk of gastric cancer: a population-based, prospective cohort study. *Int J Cancer*. 2007; **120:** 128 – 132.
**146** Gonzalez CA, Pera G, Agudo A, Palli D, Krogh V, Vineis P, et al. Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *Int J Cancer*. 2003; **107:** 629 – 634.
**147** Sasazuki S, Sasaki S, Tsugane S. Japan Public Health Center Study Group. Cigarette smoking, alcohol consumption, and subsequent gastric cancer risk by subsite and histologic type. *Int J Cancer*. 2002; **101:** 560 – 566.
**148** Inoue M, Tajima K, Yamamura Y, Hamajima N, Hirose K, Nakamura S, et al. Smoking and the risk of gastric cancer in the European Prospective Investigation. Influence of habitual smoking on gastric cancer by histologic subtype. *Int J Cancer*. 1999; **81:** 39 – 43.
**149** Jedrychowski W, Boeing H, Wahrendorf J, Popiela T, Tobiasz-Adamczyk B, Kulig J. Vodka consumption, tobacco smoking, and risk of gastric cancer in Poland. *Cancer Causes Control*. 2000; **11:** 363 – 371.
**150** Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V. Alcohol consumption, smoking, and risk of gastric cancer: case-control study from Moscow, Russia. *Int J Epidemiol*. 1993; **22:** 606 – 613.
**151** Huang XE, Tajima K, Hamajima N, Kodera Y, Yamamura Y, Xiang J, et al. Effects of dietary, drinking, and smoking habits on the prognosis of gastric cancer. *Nutr Cancer*. 2000; **38:** 30 – 36.
**152** Huang K, Sandler RS, Millikan RC, Schroeder JC, North KE, Hu J. GSTM1 and GSTT1 polymorphisms, cigarette smoking, and risk of colon cancer: a population-based case-control study in North Carolina (United States). *Cancer Causes Control*. 2006; **17:** 385 – 394.
**153** Longnecker MP, Clapp RW, Sheahan K. Association between smoking status and stage of colorectal cancer at diagnosis in Massachussets between 1982 and 1987. Cancer. 1989; **64:** 1372 – 1374.
**154** Daniel HW. More advanced colonic cancer among smokers. *Cancer*. 1986; **58:** 784 – 787.
**155** Anton-Culver H. Smoking and other risk factors associated with the stage and age of diagnosis of colon and rectum cancers. *Cancer Detect Prev*. 1991; **15:** 345 – 350.
**156** Minami Y, Tateno H. Associations between cigarette smoking and the risk of four leading cancers in Miyagi Prefecture, Japan: a multi-site case-control study. *Cancer Sci*. 2003; **94:** 540 – 547.
**157** Slattery ML, Potter JD, Samowitz W, Bigler J, Caan B, Leppert M. NAT2, GSTM-1, cigarette smoking, and risk of colon cancer. *Cancer Epidemiol Biomarkers Prev*. 1998; **7:** 1079 – 1084.
**158** Slattery ML, Samowtiz W, Ma K, Murtaugh M, Sweeney C, Levin TR, et al. CYP1A1, cigarette smoking, and colon and rectal cancer. *Am J Epidemiol*. 2004; **160:**

842 – 852.
**159** Gallicchio L, Kouzis A, Genkinger JM, Burke AE, Hoffman SC, Diener-West M, et al. Active cigarette smoking, household passive smoke exposure, and the risk of developing pancreatic cancer. *Prev Med*. 2006; **42:** 200 – 205.
**160** Larsson SC, Permert J, Hakansson N, Naslund I, Bergkvist L, Wolk A. Overall obesity, abdominal adiposity, diabetes, and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. *Br J Cancer*. 2005; **93:** 1310 – 1315.
**161** Bonelli L, Aste H, Bovo P, Cavallini G, Felder M, Gusmaroli R, et al. Exocrine pancreatic cancer, cigarette smoking, and diabetes mellitus: a case-control study in northern Italy. *Pancreas*. 2004; **28:** 451 – 452.
**162** Lin Y, Tamakoshi A, Kawamura T, Inaba Y, Kikuchi S, Motohashi Y, et al. JACC Study Group. Japan Collaborative Cohort. A prospective cohort study of cigarette smoking and pancreatic cancer in Japan. *Cancer Causes Control*. 2002; **13:** 249 – 254.
**163** Fuchs CS, Colditz GA, Stampfer MJ, Giovannucci EL, Hunter DJ, Rimm EB, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. *Arch Intern Med*. 1996; **156:** 2255 – 2260.
**164** Zheng W, McLaughlin JK, Gridley G, Bjelke E, Schuman LM, Silverman DT, et al. A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). *Cancer Causes Control*. 1993; **4:** 477 – 482.
**165** Muscat JE, Stellman SD, Hoffmann D, Wynder EL. Smoking and pancreatic cancer in men and women. *Cancer Epidemiol Biomarkers Prev*. 1997; **6:** 15 – 19.
**166** Talamini G, Bassi C, Falconi M, Sartori N, Salvia R, Rigo L,, et al. Alcohol and smoking as risk factors in chronic pancreatitis and pancreatic cancer. *Dig Dis Sci*. 1999; **44:** 1303 – 1311.
**167** Ji BT, Chow WH, Dai Q, McLaughlin JK, Benichou J, Hatch MC, et al. Cigarette smoking and alcohol consumption and the risk of pancreatic cancer: a case-control study in Shanghai, China. *Cancer Causes Control*. 1995; **6:** 369 – 376.
**168** Mulder I, Hoogenveen RT, van Genugten ML, Lankisch PG, Lowenfels AB, de Hollander AE, et al. Smoking cessation would substantially reduce the future incidence of pancreatic cancer in the European Union. *Eur J Gastroenterol Hepatol*. 2002; **14:** 1343 – 1353.
**169** Wang XL, Wang J. Smoking-gene interaction and disease development: relevance to pancreatic cancer and atherosclerosis. *World J Surg*. 2005; **29:** 344 – 353.
**170** Hirayama T. A large-scale cohort study on risk factors for primary liver cancer, with special reference to the role of cigarette smoking. *Cancer Chemother Pharmacol*. 1989; **23 (suppl):** S114 – S117.
**171** Tanaka K, Tsuji I, Wakai K, Nagata C, Mizoue T, Inoue M, et al. Cigarette smoking and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among Japanese. *Jpn J Clin Oncol*. 2006; **36:** 445 – 456.
**172** Hsing AW, McLaughlin JK, Hrubec Z, Blot WJ, Fraumeni JF Jr. Cigarette smoking and liver cancer among US veterans. *Cancer Causes Control*. 1990; **1:** 217 – 221.
**173** Jee SH, Ohrr H, Sull JW, Samet JM. Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. *J Natl Cancer Inst*. 2004; **96:** 1851 – 1856.
**174** Zhu K, Moriarty C, Caplan LS, Levine RS. Cigarette smoking and primary liver cancer: a population-based case-control study in US men. *Cancer Causes Control*. 2007; **18:** 315 – 321.
**175** Kuper H, Tzonou A, Kaklamani E, Hsieh CC, Lagiou P, Adami HO, et al. Tobacco smoking, alcohol consumption ,and their interaction in the causation of hepatocellular carcinoma. *Int J Cancer*. 2000; **85:** 498 – 502.
**176** Wang LY, You SL, Lu SN, Ho HC, Wu MH, Sun CA, et al. Risk of hepatocellular carcinoma and habits of alcohol drinking, betel quid chewing, and cigarette smoking: a cohort of 2416 HBsAg-seropositive and 9421 HBsAg-seronegative male residents in Taiwan. *Cancer Causes Control*. 2003; **14:** 241 – 520.
**177** Chen CJ, Liang KY, Chang AS, Chang YC, Lu SN, Liaw YF, et al. Effects of hepatitis B virus, alcohol drinking, cigarette smoking, and familial tendency on hepatocellular carcinoma. *Hepatology*. 1991; **13:** 398 – 406.
**178** Trichopoulos D, MacMahon B, Sparros L, Merikas G. Smoking and hepatitis B-negative primary hepatocellular carcinoma. *J Natl Cancer Inst*. 1980; **65:** 111 – 114.
**179** Trichopoulos D, Day NE, Kaklamani E, Tzonou A, Munoz N, Zavitsanos X, et al. Hepatitis B virus, tobacco smoking, and ethanol consumption in the etiology of hepatocellular carcinoma. *Int J Cancer*. 1987; **39:** 45 – 49.
**180** Lam KC, Yu MC, Leung JW, Henderson BE. Hepatitis B virus and cigarette smoking: risk factors for hepatocellular carcinoma in Hong Kong. *Cancer Res*. 1982; **42:** 5246 – 5248.
**181** Marrero JA, Fontana RJ, Fu S, Conjeevaram HS, Su GL, Lok AS. Alcohol, tobacco, and obesity are synergistic risk factors for hepatocellular carcinoma. *J Hepatol*. 2005; **42:** 218 – 224.
**182** Tzonou A, Trichopoulos D, Kaklamani E, Zavitsanos X, Koumantaki Y, Hsieh CC. Epidemiologic assessment of interactions of hepatitis-C virus with seromarkers of hepatitis-B and -D viruses, cirrhosis, and tobacco smoking in hepatocellular carcinoma. *Int J Cancer*. 1991; **49:** 377 – 380.
**183** Gelatti U, Covolo L, Talamini R, Tagger A, Barbone F, Martelli C, et al. N-Acetyltransferase-2, glutathione S-transferase M1 and T1 genetic polymorphisms, cigarette smoking, and hepatocellular carcinoma: a case-control study. *Int J Cancer*. 2005; **115:** 301 – 306.
**184** Kew MC, Dibisceglie AM, Paterson AC. Smoking as a risk factor in hepatocellular carcinoma. A case-control study in southern African blacks. *Cancer*. 1985; **56:** 2315 – 2317.
**185** Oshima A, Tsukuma H, Hiyama T, Fujimoto I, Yamano H, Tanaka M. Follow-up study of HBs Ag-positive blood donors with special reference to effect of drinking and smoking on development of liver cancer. *Int J Cancer*. 1984; **34:** 775 – 779.