Role of Opium in Esophageal Cancer: A Hypothesis

Kambiz Dowlatshahi and Richard J. Miller

Departments of Surgery and Pharmacological and Physiological Sciences, Pritzker School of Medicine, The University of Chicago, Chicago, Illinois 60637

One of the highest areas of esophageal cancer incidence in the world is in northeastern Iran where up to 180 new cases/100,000 have been recorded in Tamranian and Mazandaran villagers (10, 12). Although its use has been illegal in Iran since 1955, opium and its recycled pyrolytic product shireh are commonly smoked socially or are eaten for various bodily aches, diarrhea, and insomnia. There is now mounting evidence that the widespread use of such narcotics, particularly in the high-incidence regions, is associated with the development of esophageal cancer (5, 8, 20). One argument that has been put forward against the carcinogenicity of opium and its pyrolyzed products is that its rapid transit through the esophagus will not allow the potential carcinogen to act upon the mucosa (20).

The association between opium usage and esophageal cancer in Iran was first noted during a 2-year clinical observation and case documentation by Dowlatshahi et al. (5) between 1974 and 1976, in which 61% of males and 25% of females among 126 patients with documented esophageal cancer gave a 5- to 20-year history of opium addiction antecedent to the onset of their symptoms. The sex ratio of the cancer incidence in this group was also 3:1. Brownish black particles of burnt opium were noted on the esophageal mucosa, and the odor of the compound was detected during endoscopic examination of these patients. During an endoscopic survey for early detection of esophageal carcinoma in an adjacent town, Crespi et al. (3) reported 80% chronic esophagitis among 430 mainly asymptomatic adults. Informal local inquiry by one of the authors and epidemiological studies by the International Agency for Research on Cancer revealed a widespread habit of opium usage in the high-incidence esophageal cancer belt, as well as the presence of morphine metabolites in the urine of adults in this region (20). Hewer et al. (8) tested the mutagenicity of the pyrolyzed opium, a tarry residue collected from the pipe of addicts called sukhteh, and reported significant activity in Salmonella typhimurium strains TA98 and TA100 in the presence of rat liver microsomes. This observation has now been substantially confirmed by International Agency for Research on Cancer investigators who pyrolyzed opium and its major alkaloid morphine under laboratory conditions closely mimicking the addict’s pipe (12). It is suggested that heterocyclic aromatic hydrocarbons and primary aromatic amines are the major active principles of the displayed mutagenicity. This concept has been further substantiated by Perry et al. (16), who demonstrated greater induction of sister chromatid exchange by products of pyrolyzed opium.

Until recently, it was thought that the motility of the esophagus and its lower sphincter function were controlled by the classical neurotransmitters acetylcholine and norepinephrine as well as by endogenously produced hormones such as steroids and exogenous substances such as alcohol and caffeine. It has now become apparent that the intestinal motility is also influenced by noncholinergic, nonadrenergic nerves. The opioid peptides called enkephalins are found in high concentrations in neurons of the myenteric plexus of the esophagus and the lower esophageal sphincter (19, 21). Enkephalin-containing processes increase in frequency in the distal portion of the esophagus, particularly in the muscularis mucosa. This innervation implies some role for these endogenous opiates in the regulation of esophageal function. Five distinct types of opiate receptors have been demonstrated in the lower esophageal sphincter of opposum (18). Recently, we have investigated the influence of morphine, the main constituent of opium, on the motility of the distal esophagus and the sphincter function in humans (6). We found that morphine inhibits the relaxation of the lower esophageal sphincter, thus impeding the passage of esophageal contents into the stomach. In addition to its opiate receptor-mediated inhibitory influence on esophageal peristalsis, crude opium contains 1% papaverine (14). This nonopoid alkaloid has a direct and nonspecific relaxant effect on the smooth muscle which forms the distal two-thirds of the esophagus. If unaltered through combustion in the addict’s pipe, papaverine should decrease the frequency and the force of esophageal peristalsis. Thus, there is certainly evidence for the alteration of esophageal motility by both exogenous and endogenous opiates. The pharmacology of this system is as yet poorly described. However, the profusion of enkephalin-containing nerves in these areas attests to the important role they may play.

There is evidence to suggest that prolonged deficiency of specific micronutrients such as vitamin A, riboflavin, and nicotinic acid as well as trace elements such as zinc, molybdenum, magnesium, and iron render the esophageal mucosa vulnerable to carcinogenic insult (9, 10, 15, 22, 23). The staple diet of the high-incidence esophageal cancer Mazandarani and Turkman villagers in northeast Iran is high in bread and tea and low in vitamin A, riboflavin, and vitamin C (9, 10). In contrast, the inhabitants of villages in the low-incidence regions of the Caspian littorals consume a well-balanced diet. The hair zinc content of the villagers from the high-incidence regions was shown to be significantly lower in comparison with controls from Tehran and Baltimore (15). Animals on zinc-deficient diets developed esophageal mucosal hyperplasia and parakeratosis reversible on zinc supplementation (1, 4, 7). Similar correlations between dietary deficiencies and the incidence of esophageal cancer have been noted in Transkei, South Africa (2). A recent case-control study of esophageal cancer among blacks in Washington, DC, revealed that the diet of esophageal cancer patients was significantly

1 Supported by U.S.P.H.S. Grant DA 02121.
2 To whom requests for reprints should be addressed, at: Department of Surgery, University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637.
3 Alfred P. Sloan Fellow.

Received 7/30/84; revised 10/22/84, 11/21/84; accepted 12/20/84.
deficient in protein, dairy products, vegetables, and fresh fruit (16, 24).

From the evidence presented above, it appears possible that opium decreases esophageal peristalsis through direct action of papaverine on the smooth muscle and inhibits the relaxation of the lower esophageal sphincter via its morphine constituent. The ensuing relative stasis allows a potential swallowed carcinogen to have prolonged contact with the esophageal mucosa and enhance neoplasia. This would be particularly true if the mucosa is vulnerable as a result of chronic malnutrition.

REFERENCES

Role of Opium in Esophageal Cancer: A Hypothesis

Kambiz Dowlatshahi and Richard J. Miller


Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/45/4/1906.citation