Klingsøyr et al. (1) found an increased risk of depression associated with smoking. They attributed this to the inhibition of monoamine oxidase B-affecting neurotransmitters such as serotonin (1). They also examined alternative explanations, including selection bias, recall bias, unmeasured confounding variables, indirect causation, and reverse causation.

Tobacco smoke increases cancer risk through multiple molecular mechanisms (2, 3). It is not inconceivable that smoking might increase the risk of depression though multiple mechanisms as well.

DNA methylation, the addition of a methyl group to cytosine in the dinucleotide sequence 5′CpG, plays a role in silencing gene expression (4). A study of monozygotic twins found that epigenetic markers shift throughout the life span (5), suggesting that they may be influenced by the environment into adulthood.

Aberrant DNA methylation has been suspected of contributing to a number of psychiatric disorders, including depression (4). Findings of recent studies are consistent with the idea that aberrant methylation of DNA may play a role in depression. In a rat model, environmental factors produced a difference in DNA methylation status which correlated with differences in behavioral response to stress (6). Low folic acid levels result in aberrant methylation of DNA (4). Low folic acid levels have also been associated with increased risk of depression. Arsenic increases bladder cancer risk by promoting aberrant methylation of DNA (3). Higher levels of arsenic (≥2 μg/liter) in drinking water have been associated with an increased incidence of depression (7).
Smoking increases cancer risk in part by promoting the aberrant methylation of DNA (3). Now, Klungsøyr et al. have found that smoking increases the risk of depression (1).

A more basic question is: Since aberrant methylation of DNA has been suggested to be involved in psychiatric disorders ranging from schizophrenia to depression, do certain carcinogens that cause aberrant methylation of DNA also increase the risk of psychiatric disorders through that mechanism (3, 4)?

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