

Low levels of serum bilirubin spell higher lung cancer risk for male smokers

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Elevated levels of bilirubin in the blood get attention in the clinic because they often indicate that something has gone wrong with the liver. Now researchers have found that male smokers with low levels of the yellow-tinged chemical are at higher risk for lung cancer and dying from the disease.

A team led by researchers at The University of Texas MD Anderson Cancer Center reported its findings in a late-breaking abstract at the AACR Annual Meeting 2013 in Washington, D.C.

"Our study indicates [male smokers](#) with low levels of bilirubin are a high-risk group that can be targeted with [smoking cessation](#) help, low-dose spiral CT screening of their lungs and other preventive measures," said senior author Xifeng Wu, M.D., Ph.D., professor and chair of MD Anderson's Department of Epidemiology and the Betty B. Marcus Chair in [Cancer Prevention](#).

[Lung cancer](#) usually is diagnosed at a late stage, when tumors are inoperable and treatments largely ineffective. The overall five-year survival rate is 15 percent, but it falls to 5 percent for stage 3 [lung cancer patients](#) and 1 percent for those with stage 4 disease.

Spiral CT scans catch cancer early, biomarker could reduce false positives

The National Lung Screening Trial found that low-dose spiral computed

tomography screening reduces mortality among [heavy smokers](#) by 20 percent. However, 95 percent of growths found by [spiral CT](#) are false positives, a barrier to large-scale screening.

"Validated biomarkers are urgently needed to improve [risk prediction](#) for lung cancer and to reduce false positives, shifting the balance toward more effective and efficient [CT screening](#) for [cancer detection](#)," Wu said.

The researchers started with an objective analysis of levels of metabolites—substances produced during metabolism. Bilirubin is produced during the breakdown of old blood cells.

They analyzed 60 samples divided into three groups known as "trios"—normal controls, early stage and late stage non-small cell lung cancer patients. The top three metabolites were validated in two more groups of 50 and 123 trios.

When bilirubin emerged as the most significant metabolite, another validation study was done in a prospective cohort of 435,985 people with 208,233 men in Taiwan.

Men were divided into four groups according to their serum bilirubin levels. Lower bilirubin level was associated with significantly higher rates of both lung cancer incidence and mortality.

In the Taiwanese cohort, the incidence rate per 10,000 person-years in men was 7.02 for those in the lowest bilirubin quartile (.68 mg/dL or less), compared to 3.73 in the highest quartile of bilirubin level (1.12 mg/dL or more). The mortality rate per 10,000 person-years was 4.84 for the lowest level compared with 2.46 in the highest bilirubin quartile.

Next step: Establish a risk prediction model in heavy

smokers

Bilirubin makes sense as a protective agent because of its anti-oxidant, anti-inflammatory and anti-proliferative effects. "It's plausible that bilirubin protects against lung cancer by scavenging free radicals and carcinogens associated with smoking," said study presenter Fanmao Zhang, a doctoral candidate in epidemiology.

Indeed, a Belgian study showed that bilirubin in the high normal range lowered cancer mortality in men. A study in the United Kingdom showed higher bilirubin levels in the normal range were associated with lower risks of chronic obstructive pulmonary disease, lung cancer and all-cause mortality. Neither of those studies stratified their analysis of bilirubin by smoking status.

"We expected that bilirubin might be protective, but our finding that bilirubin levels affect only smokers was somewhat of a surprise," Wu said. "Our discovery that low levels increase lung [cancer risk](#) is unique."

Smokers in the two middle cohorts of bilirubin levels also had higher lung cancer risk than those in the highest quartile. As an objective risk index for lung cancer and all-cause mortality, low levels of bilirubin should send an urgent message to quit smoking, said Chi Pang Wen, M.D., Ph.D., co-lead author from National Health Research Institutes, Taiwan.

The next step, Wu said, is to evaluate the predictive value of serum bilirubin in heavy smokers and to establish a risk prediction model that incorporates bilirubin and other biomarkers with clinical and epidemiological data to improve the efficiency of lung cancer risk prediction.

Provided by University of Texas M. D. Anderson Cancer Center

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