Study: Mice that vaped nicotine for a year had big increase in tumor growth

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New research in mice suggests that long-term exposure to vaping liquids that contain nicotine greatly increases the risk of cancer.

After breathing in the vapor for 20 hours a week for more than a year, 22.5% of the mice had cancerous tumors in the lining of the lungs, and 57.5% developed growths in their bladder tissue that can be precursors to cancer.

Meanwhile, only 5.6% of mice in a control group that breathed only filtered air wound up with lung tumors, and none of them had growths in their bladders. In addition, a group of mice exposed to aerosolized vaping chemicals without nicotine developed no lung tumors, and just 6.3% of them had precancerous bladder growths.

The scientists who conducted the study stressed that much more research is needed to know whether vaping leads to cancer in humans. But they hope their findings, published Monday in the journal *Proceedings of the National Academy of Sciences*, will make people think twice before trying e-cigarettes, which are widely perceived by teenagers and young adults as a safe alternative to smoking.

"Right or wrong, millions of young people are using these right now, and the long-term, population-wide studies won't be able to report out results for another decade," said study leader Moon-Shong Tang, an environmental health expert at NYU School of Medicine.

"We needed credible evidence to guide people in their choices, and it is unambiguous that nicotine alone will cause damage to the cells that make up organs, including lungs," said Tang, who has studied how tobacco smoke promotes cancers of the lung and bladder. "Now, we can try to find measures to prevent incidents of e-cigarettes causing cancer."

Vaping has been linked to heart attacks, seizures and burns from exploding devices. And a growing outbreak of at least 1,080 vaping-related lung injuries serves as a stark reminder that it's too soon to know whether e-cigarettes are a safe alternative to smoking.

To get a better idea of the long-term effects of nicotine, Tang and his collaborators exposed 45 mice to an aerosol of nicotine dissolved in isopropylene glycol and vegetable glycerin, a common vehicle for vaping liquids. Another group of 20 mice was exposed to the same vehicle without nicotine. For 54 weeks, the animals were subjected to the aerosol mixes for four hours per day, five days per week.

A third group of 20 mice spent their time in a room with ambient filtered air. (The study was limited to 54 weeks in order to minimize the effects of age-related cancers that could have cropped up occurred regardless of exposure to e-cigarette vapor.)

Five mice in the group exposed to nicotine died over the course of the year. So did two of the mice in each of the other groups.

When the 54 weeks were up, the remaining animals were killed and the researchers examined their tissues. Nine of the 40 mice in the nicotine group had tumors in their lungs, compared with none of the 18 mice that breathed the nicotine-free aerosol and one of the 18 mice exposed to filtered air. (Tang said he wasn't surprised that a tumor was found in the control group, since mice typically have increased rates of lung cancer.)

In addition, the researchers found that 23 of the 40 mice that inhaled the vapor with nicotine developed bladder hyperplasia, an out-of-control cell reproduction in the lining of the bladder that often precedes cancer. That compares with 1 out of 16 mice that inhaled vapor without nicotine and zero out of 17 mice that breathed filtered air. (Tissue samples from three of the mice were accidentally destroyed and could not be included in the analysis.)

The differences were large enough for the researchers to conclude that the aerosolized vaping liquid with nicotine was responsible for the increased risk of tumors. For instance, the mice that inhaled the nicotine

mixture were eight times more likely to develop lung tumors than the mice in the other two groups that weren't exposed to nicotine.

"This is compelling, and very scary," said Dr. Mark Litwin, the chair of UCLA's Department of Urology. "When the instructions encoded in DNA get mangled, the cells go on a craze and continue multiplying, unable to control themselves. That's a hallmark of cancer. And at a glance, this already looks like precancer tissue."

The researchers also found that a few of the mice exposed to e-cigarette vapor—with or without nicotine—developed abdominal or skin tumors, while none of their counterparts in the filtered-air group did. However, those differences were small and could have been due to chance.

The work was funded by the National Institutes of Health.

On a molecular level, the findings make sense. Tang's team published research last year showing that, when nicotine is introduced to mammalian cells, innate molecules called nitrosonium ions react with the nicotine to form carcinogens—in both mice and humans.

"We can't say that e-cigarettes definitively cause human cancer, but the mechanism at play here is very clear: The same carcinogens are being produced that other studies have shown cause human cancer," Tang said. "We can extrapolate that, with e-cigarettes, you'll cause damage in your genetic material, and damage your cells—and that will accumulate the longer you smoke."

Smoke from e-cigarettes "must be more thoroughly studied before it is deemed safe or marketed that way," he added.

The study had several limitations, the authors acknowledged. It included a small number of mice, and they were surrounded by the vapor rather

than inhaling it the way human e-cigarette users would.

Dr. Herbert Lepor, a study author and the chair of urology at NYU's Langone Health, said the team plans to use a larger group of mice to test short and long periods of exposure. The researchers also plan to take a closer look at the genetic changes associated with inhaling e-cigarette smoke.

Experts agree that the new study doesn't answer the swirling questions surrounding the current outbreak of lung conditions linked to vaping. But it does validate worries about the long-term effects of e-cigarettes.

"Teenagers will tell you that vaping is safer because it eliminates all the carcinogenic parts of a cigarette," Litwin said. "As it turns out, that might not be the case."

More information: Moon-shong Tang el al., "Electronic-cigarette smoke induces lung adenocarcinoma and bladder urothelial hyperplasia in mice," *PNAS* (2019). www.pnas.org/cgi/doi/10.1073/pnas.1911321116