MRI every 6 months was associated with an absence of interval cancers and with high sensitivity/specificity for detecting tumors smaller than 1 cm. Led by Olufunmilayo I. Olopade, MD, a hematologist–oncologist at the University of Chicago Hospitals, the authors concluded that their results "support this screening strategy as a viable alternative to prophylactic mastectomy." According to Domchek, women under surveillance at the Perelman School of Medicine get staggered mammograms and MRI 6 months apart.

When women complete (or forgo) child rearing, chemoprevention alone or in combination with oophorectomy may also offer an alternative to mastectomy. But according to Davidson, the evidence for chemoprevention benefits in BRCA-positive women derives almost entirely from studies showing that agents such as tamoxifen and raloxifene reduce the risk of tumors in the other breast in women who have already had breast cancer. In 2000, for instance, Steven Narod, MD, a fellow of the Royal Society of Canada in Toronto, published findings in *The Lancet* showing that tamoxifen halves the risk of cancer in the opposite breast in women with BRCA1 and BRCA 2 mutations. And this year, Kelly-Anne Phillips, MD, of the Peter MacCallum Cancer Centre in Victoria, Australia, published virtually identical risk reductions in the *Journal of Clinical Oncology*. Davidson said that scientists have tried to look at primary prevention of the first tumor in BRCA-positive individuals (for instance, through the National Surgical Adjuvant Breast and Bowel Project's P1 trial), but since the mutations are so rare, the results so far lack statistical power. Still, Davidson asserted that results from the secondary prevention trials should translate equally to the prevention of primary cancers, even regardless of their estrogen receptor (ER) status. Tamoxifen and raloxifene are both geared toward ER-positive cancer cells, but Davidson pointed out that these cells can become ER negative over time. Moreover, tumors are often heterogeneous with respect to their ER-positive or -negative composition.

"There is some evidence that chemoprevention can prevent ER-negative tumors, or tumors that become ER negative later," Davidson said. "But the evidence isn't strong and we need more work to explain why that might be happening."

Adding oophorectomy to chemoprevention should boost primary cancer prevention even further, because tamoxifen, for instance, does not affect the ovaries, whereas oophorectomy reduces the risk of ovarian cancer by roughly 90% and reduces circulating hormone levels that can promote growth of breast tumors. Narod's 2000 paper showed that oophorectomy combined with tamoxifen reduced breast cancer risk by 84%, a benefit that, Offit said, approximates that achieved with mastectomy. Later studies have not shown this same degree of combined effect, he said, "but the evidence is clear from these studies that tamoxifen as well as oophorectomy separately confer protection against breast cancer risk in BRCA mutation carriers."

Survival Benefits

Moreover, oophorectomy can reduce not only cancer risk but also cancer mortality. Experts say it's logical to assume that by cutting the risk of breast cancer by more than 80%, mastectomy saves the lives of BRCA-positive individuals, even though its survival benefits have never been explicitly documented. However, Domchek showed that oophorectomy is associated with roughly 60% reductions in mortality from both ovarian and breast cancer. The *Journal of the American Medical Association* published her findings in 2010.

Jolie wrote that she chose mastectomy to minimize her cancer risks as much as possible. That's also true for Stacy Jacobsen, a 42-year-old mother of two, who responded to BRCA-positive status by having both her breasts and ovaries removed in 2011.

"I'm by nature an anxious person, and I wanted to get my odds down as low as I could get them," she said. "My doctors were comfortable with surveillance: If I got cancer they could deal with it early on. But I didn't want to go through that worrying cycle every 6 months."

According to Larry Norton, MD, deputy physician in chief for Breast Cancer Programs at MSKCC, decisions on surgery may soon be aided by ongoing efforts to identify other genes that exacerbate BRCA risks. Studies at MSKCC this year will focus on 15 modifying single-nucleotide polymorphisms that, preliminary evidence suggests, can boost breast cancer risks among BRCA2-positive women from 50% to 80%.

Meanwhile, Jacobsen is happy with her decision. "I feel fabulous," she said. "For me, this was the right choice. I feel that my cancer risks are super low."

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No Clear Link Between Passive Smoking and Lung Cancer

By Judy Peres

A large prospective cohort study of more than 76,000 women confirmed a strong association between cigarette smoking and lung cancer but found no link between the disease and secondhand smoke.

"The fact that passive smoking may not be strongly associated with lung cancer points to a need to find other risk factors for the disease [in nonsmokers]," said Ange Wang, the Stanford University medical student who presented the study at the June

2013 meeting of the American Society of Clinical Oncology in Chicago.

Investigators from Stanford and other research centers looked at data from the Women's Health Initiative Observational Study (WHI-OS). Among 93,676 women aged 50–79 years at enrollment, the study had complete smoking and covariate data (including passive smoking exposure in childhood, adult home, and work) for 76,304 participants. Of those, 901 developed lung cancer over 10.5 mean years of follow-up.

The incidence of lung cancer was 13 times higher in current smokers and four times higher in former smokers than in never-smokers, and the relationship for both current and former smokers depended on level of exposure. However, among women who had never smoked, exposure to passive smoking overall, and to most categories of passive smoking, did not statistically significantly increase lung cancer risk. The only category of exposure that showed a trend toward increased risk was living in the same house with a smoker for 30 years or more. In that group, the hazard ratio for developing lung cancer was 1.61, but the confidence interval included 1.00, making the finding of only borderline statistical significance.

"To our knowledge, this is the first study to examine both active and passive smoking in relation to lung cancer incidence in a complete prospective cohort of US women," Wang reported. "The findings support continued need for investment in smoking prevention and cessation, research on passive smoking, and understanding of lung cancer risk factors other than smoking."

Jyoti Patel, MD, of Northwestern University School of Medicine said the findings were not new.

The study "mimics the numbers we've known," she said. "In the existing literature, an active smoker who smokes two packs a day for 30 years has a 60-fold-higher risk of lung cancer than a never-smoker, and a never-smoking woman living with a smoking husband for 30 years has a twofold-higher risk.

"Passive smoking has many downstream health effects—asthma, upper respiratory infections, other pulmonary diseases, cardiovascular disease—but only borderline increased risk of lung cancer," said Patel. "The strongest reason to avoid passive cigarette smoke is to change societal behavior: to not live in a society where smoking is a norm.

"It's very reassuring that passive smoke in the childhood home doesn't increase the risk of lung cancer [in this study]," said Patel. "But it doesn't decrease the need for us to have strong antismoking measures. There are very few never-smokers in smoking families."

A large body of research has linked passive smoking to lung cancer, as well as to coronary heart disease, asthma, emphysema, respiratory infections, sudden infant death syndrome, low birth weight, and childhood ear infections. According to the Centers for Disease Control and Prevention, secondhand smoke is responsible for 46,000 heart disease deaths and 3,400 lung cancer deaths among US nonsmoking adults each year. But many studies that showed the strongest links between secondhand smoke and lung cancer were case–control studies, which can suffer from recall bias: People who develop a disease that might be related to passive smoking are more likely to recall being exposed to passive smoking.

"Passive smoking has many downstream health effects—asthma, upper respiratory infections, other pulmonary diseases, cardiovascular disease—but only borderline increased risk of lung cancer."

So does secondhand smoke cause lung cancer or not? "We can't say it's not a risk factor," said Wang.

Heather Wakelee, MD, associate professor of medicine and oncology at Stanford and one of the study's senior investigators, explained why. WHI-OS had only 901 cases of lung cancer, and only 152 of those occurred in never-smokers. "It's hard to say anything conclusive with such small numbers," said Wakelee.

Another problem is that measuring exposure to passive smoke is hard. "Living with a husband who smokes a lot with the windows closed is reported the same as living with one who smokes a little, mostly on the porch," said Wakelee. (The study measured passive smoking in years, not pack-years.)

Moreover, of the nearly 40,000 nonsmokers in the WHI-OS, only about 4,000 reported no exposure to cigarette smoke. "That means almost everybody had passive-smoking exposure," said Wakelee, "so it's very hard to say that that exposure is causing the problem—it's hard to tease out a difference.


Jyoti Patel, MD

"We don't want people to conclude that passive smoking has no effect on lung cancer," she said. "We think the message is, this analysis doesn't tell us what the risk is, or even if there is a risk."

Debbie Winn, PhD, deputy director of the Division of Cancer Control and Population Sciences at the National Cancer Institute, said it might be useful to "join up with other cohorts and ask the same question. You need cohorts that together can yield many thousands of cases and controls."

Meanwhile, said Winn, the International Agency for Research on Cancer (as well as NCI) has said unequivocally that passive smoking is a cause of lung cancer. "You shouldn't conclude from this study that it isn't," she said.

Gerard Silvestri, MD, of the Medical University of South Carolina, a member of NCI's PDQ Screening and Prevention Editorial Board, welcomed the WHI-OS study for its focus on women and for emphasizing that smoking greatly increases their risk of lung cancer.

"More women will die of lung cancer this year than of all other female

cancers—breast, ovarian, cervix, and uterine—combined," he said. "A lot of women have missed that message. And it's an incredibly important message for young female smokers. They are the most at-risk group now because they have made the connection between smoking and weight control."

However, Silvestri finds some reassurance in the passive-smoking findings. "We can never predict who is going to develop lung cancer," he said. "There are other modifiers. But you can say, with regard to passive smoke, it's only the heaviest exposure that produces the risk. We kind of knew that before, but it's a little stronger here."

"We've gotten smoking out of bars and restaurants on the basis of the fact that you and I and other nonsmokers don't want to die," said Silvestri. "The reality is, we probably won't."

According to data compiled by Americans for Nonsmokers' Rights, 24 U.S. states and 575 municipalities and counties have laws banning smoking in all nonhospitality workplaces, restaurants, and bars; 36 states prohibit public smoking to some degree. Nearly 200 local governments also ban smoking in private units of multiunit housing.

Internationally, 91 nations have enacted some sort of antismoking laws.

Asked whether a waitress who spent 15 years working in a smoky bar should feel reassured, Wakelee said, "Certainly, if you look just at this study and ignore other data. But you can't really ignore all the other data or ignore all the health risks linked to that exposure."

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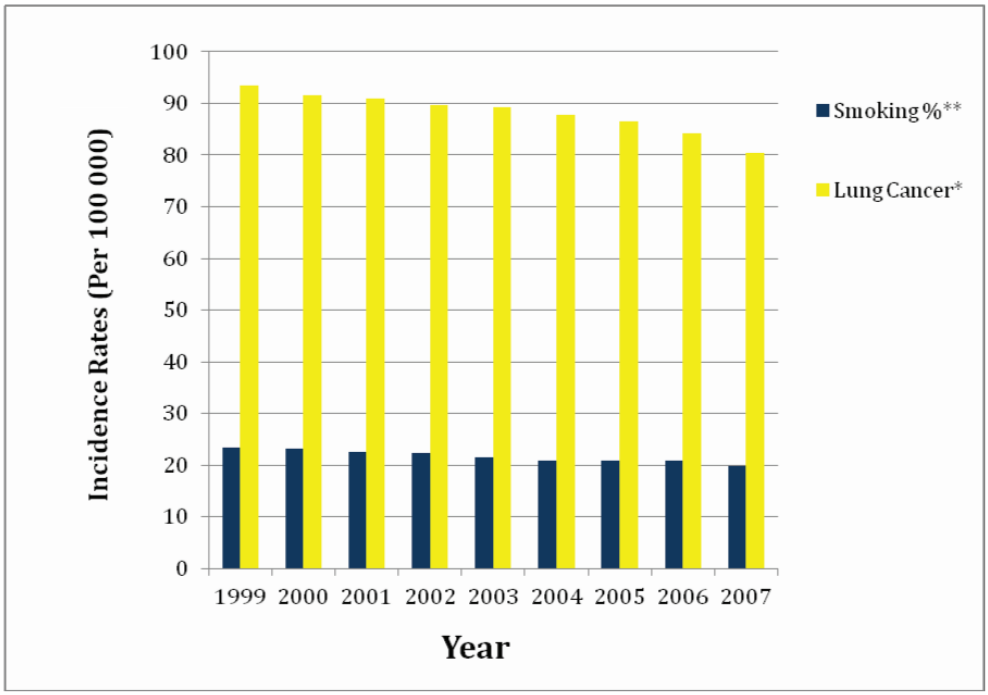
STATBITE

Smoking Rates vs Lung Cancer Incidence (1999–2007)



Source: *National Program of Cancer Registries, CDC
**CDC

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