Epidemiologists Find Association Between Gene Variants and Smoking

by Sunni Hosemann

A molecular genetics case-control study, led by Margaret Spitz, M.D., chairman of The University of Texas M. D. Anderson Cancer Center Department of Epidemiology, found a statistically significant relationship between carrying specific variant genotypes of a dopamine receptor gene and the propensity to smoke. The findings expand earlier studies suggesting heredity affects initiation and continuation of smoking.

By linking genetic traits with a propensity for smoking, researchers are putting together the puzzle of smoking resilient to cessation efforts.

In an ongoing study of 157 patients with lung cancer and 126 control subjects matched for age, sex, ethnicity, and smoking status, Dr. Spitz and colleagues found that subjects with variant alleles in a dopamine receptor gene were more likely to be smokers, to have started smoking at a younger age, and to have tried to quit fewer times than other subjects with normal wild-type genotypes. The dopamine receptor gene is implicated in the reward pathway through which nicotine exerts its addictive effect.

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Researchers have been interested in dopamine receptors and their possible connection with addiction and substances of abuse since the late 1980s. The D2 dopamine receptor gene Spitz and coworkers studied is believed to govern the availability of dopamine, which acts as a neurotransmitter by which such compounds as nicotine, alcohol, and cocaine create sensations of pleasure or reward in the brain. Ernest P. Nobel, Ph.D., M.D., and coworkers, in well-publicized studies, identified the alleles as important in alcoholism and found them associated more commonly with smokers than with study subjects who had never smoked.

Individuals with these variants may well have fewer dopamine receptors, constituting a deficiency in the natural dopamine effect. Researchers suggest that this has the effect of enhancing the reward from nicotine and similar addictive substances.

Dr. Spitz and her colleagues consider their study preliminary and call it “hypothesis-generating” rather than conclusive and have called for larger studies to replicate and build on their findings. Small sample size, including the low number of subjects who never smoked, and recall bias may have affected results, according to the researchers. Dr. Spitz said the study’s importance lies in the potential for identifying those at risk and for tailoring both chemical and behavioral interventions to a person’s genetic profile.

Research is under way now at M. D. Anderson to study the effectiveness of existing drugs and other types of interventions, and it is also probable that entirely new target agents will be developed. Directing the research is Paul Cinciripini, Ph.D., of the Department of Behavioral Science, a coauthor on the Spitz study.

Robert Chamberlain, Ph.D., another of Dr. Spitz’s study collaborators, also points out that “in addition to targeting our interventions, it may be that in the future we’ll also be able to direct our resources more effectively as well. It’s possible that we’ll be able to identify individuals who really need more intensive help, perhaps HMOs and other payers will be willing to pay for it.”

"Actually, we already have clues to identifying individuals who are susceptible," said Dr. Chamberlain. Key indicators include use of tobacco at an early age, the great importance of the first cigarette in the morning, the number of unsuccessful attempts to quit, continuing to smoke even when sick in bed, extreme difficulty abstaining in places where smoking is banned, and waking in the night in need of a cigarette. Chamberlain adds, "Some of these individuals may also have suffered severe symptoms during quit attempts. Remember that they have a different physiological need. Their cells absolutely crave nicotine."

Many of the individuals identified as very vulnerable are expected to be the ones who share the genetic characteristics named in the study. Simply identifying these individuals may be helpful. Dr. Chamberlain noted, “Many of us have admonished all of our patients to quit and are frustrated by the patient who just can’t seem to do it. It helps to recognize that this patient may in fact be not weak or recalcitrant but in fact more in need of our consoling advice and referral to more intensive interventions than others.”

The study findings suggest interventions that might make sense to add to a physician’s smoking cessation repertoire.

“Antidepressants are a possibility to be considered,” says Dr. Spitz.

One of the effects of dopamine is to relieve depression. Whether some smokers are unwittingly treating their own depression is unknown. Other researchers have found repressive mood and a history of depression to be associated with smoking and to be more common among smokers than nonsmokers, according to Dr. Spitz and her coauthors. No studies have linked the A1 or B1 genotypes to depression. However, in studies conducted by Dr. Cinciripini, it was clear that negative mood during quit attempts was the most powerful predictor of failure.

But which ones to use? Dr. Cinciripini’s group used a serotonin reuptake inhibitor, which also affects dopamine levels. They found that while people on the drug did better than those on placebo, it was much less effective in the group with the A1 allele. “This actually surprised us,” said Dr. Cinciripini, “and probably suggests that other antidepressant agents may be better for this group or that they may lack the capacity to respond to higher levels of dopamine or serotonin.”
Studies in Cancer Prevention and Health Care After Cancer Therapy Focus on Specific Needs

Clinical trials currently in progress at The University of Texas M. D. Anderson Cancer Center include the following. Contact the M. D. Anderson Information Line or the M. D. Anderson clinical trials listing on the World Wide Web (see numbers and addresses below) for more information.

- **Individualized relapse prevention among women smokers (BS96-184).**
  **Researcher: David Wetter, Ph.D.**

- **Computer-delivered treatment for smoking cessation (BS96-270).**
  **Researcher: David Wetter, Ph.D.**

  These cancer prevention studies are open to men and women 18 to 70 years of age. In them, Assistant Professor David Wetter is using transdermal nicotine patches, a computer, and counseling to ensure smoking cessation success. Participants must have been smoking at least 10 cigarettes per day for the last year and have carbon monoxide levels ≥10 parts per million in exhaled air. They must agree to abstain from all tobacco and nicotine use (except for the supplied patches) and have no history of heart disease that contraindicates nicotine patch use. Used in these studies is a wallet-size handheld computer that transmits supportive cessation messages to reinforce efforts to quit.

- **Ecogenetic study of lung cancer (CPN91-001).**
  **Physician: Margaret Spitz, M.D.**

  In this protocol, Professor Margaret Spitz, M.D., is studying lifestyle and biologic associations with lung cancer. Participants must be newly diagnosed with lung cancer but must not have begun treatment. Participation involves an interview and providing a blood sample.

- **Skeletal health preservation in postmenopausal women with history of breast cancer: Development of effective long-term strategies using currently available nonhormonal treatments (randomized study) (DM96-215).**
  **Physician: Rena V. Sellin, M.D.**

  In this study of nonhormonal treatment to prevent bone loss, subjects will take calcium alone or in combination with alendronate (Fosamax) or calcitonin (Miacalcin). Postmenopausal patients who formerly had breast cancer who are being seen annually at M. D. Anderson are eligible for participation. Patients should have completed treatment with adjuvant tamoxifen and have a lumbar spine bone mineral density of 0.8–1.0 g/cm².

- **Estrogen replacement therapy in women with a background of breast cancer (DM90-063).**
  **Physician: Rena V. Sellin, M.D.**

  To participate in this study, which includes treatment with conjugated estrogens, women must have no evidence of disease but must have had stage I or II breast cancer previously. If their breast cancer was not estrogen responsive, they must have had no evidence of disease for two years, but if their tumors were responsive to estrogen or if the estrogen-responsive status is not known, they must have been free of disease for 10 years. They must be >16 years of age and free of other illness or disease, including benign proliferative breast disease. They must be amenorrheic as a result of ovarian failure and have no history of thromboembolic events, acute myocardial infarction, or angina.

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For more information about these clinical trials, physicians or patients should call the M. D. Anderson Information Line. Those in the United States, call (800) 392-1611; those in Houston or outside the United States, call (713) 792-6161. Visit the M. D. Anderson Cancer Center clinical trials Web site at http://www.clinicaltrials.org.
Kicking the Tobacco Habit: The Five Commandments

Ready to quit smoking? Here are five commandments to follow to help you stick to your resolution to quit. It begins and ends with you.

I Thou shalt know thyself.

Only you know why quitting smoking is important to you. Improving your health and saving your money are two good reasons. But maybe you want to quit for more personal reasons—because your granddaughter asked you to or because you are embarrassed to be the only one in your group still smoking. You, too, are the only one who knows why you keep smoking. Do you smoke to relax, to socialize, or to fend off hunger? Make a list of these reasons so that you can understand what triggers your urge to smoke.

II Thou shalt choose a method.

Quitting may be done cold turkey or gradually and with or without the aid of medications or a nicotine replacement.

Effective but difficult, quitting cold turkey means never using tobacco again once the decision is made to quit. Quitting gradually will improve your health as you taper the amount of tobacco you consume; however, it will take longer to get results. In addition, prolonging exposure to harmful elements in tobacco smoke ensures a significant health risk persists.

Nicotine replacement therapy uses a skin patch, chewing gum, nasal spray, or a nicotine inhaler to assist in quitting. These products reduce nicotine cravings and withdrawal symptoms without exposing the user to tobacco’s harmful effects. They allow smokers to focus more effectively on breaking the habit. Nicotine replacement therapy delivers nicotine to the bloodstream at a lower and slower rate, helping smokers break the addiction.

The patch supplies a convenient and regularly supplied nicotine replacement. Gum and nasal spray may be more effective for a diverse group of quitters concerned about epistemic cravings and weight gain; however, when gum and spray are discontinued, weight gain can still occur. Research has shown that gum is less effective than patches when minimal or no counseling is included.

Never smoke while using nicotine replacement products. As an aid in the quitting process, some physicians prescribe an antidepressant alone or in combination with nicotine replacement.

III Thou shalt commit.

Make a commitment to quit after identifying the reasons for wanting to stop, understanding your personal reasons for continuing, and choosing a method for quitting that you think will work for you. Schedule quitting on the calendar. Create and sign a contract with yourself that commits you to quitting. Post it in a highly visible spot at work, at home, or at school to remind you of your commitment.

IV Thou shalt prepare to quit.

Planning can ease the transition to nonsmoking status.

- Remove lighters, ashtrays, and other smoking paraphernalia from living and working spaces.
- Review your list of reasons for smoking, and identify alternative activities for those that trigger the desire for tobacco.
- Choose alternative behaviors such as exercise to substitute for smoking. Carry a straw or a pen to replace the cigarettes once held.
- To increase chances of long-term abstinence, enroll in a counseling program that emphasizes problem solving.
- Begin an exercise program.
- Enlist friends and family in helping you achieve your goal.

V Thou shalt be true to yourself and your commitment to quit.

Always remember why you—not anyone else—have chosen to quit. Keep your commitment to quit. The benefits are immeasurable. When you succeed, reward yourself. Remember that not smoking is habit-forming, too.

For advice on quitting, call Martha Berry, smoking cessation program senior counselor, at M. D. Anderson’s Cancer Prevention Center, (713) 745-8040. Or, for information from the National Cancer Institute’s Cancer Information Service, call (800) 4-CANCER.

For more information, contact your physician or contact the M. D. Anderson Information Line:

📞 (800) 392-1611 within the United States, or
📞 (713) 792-6161 outside the United States.

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Clearing the Smoke:

New Antitobacco Initiatives Include Clinic and Computers

by Alison Ruffin

The M. D. Anderson Cancer Prevention Center has launched a new tobacco cessation clinic, staffed by a full-time smoking cessation counselor, Martha Berry.

The Tobacco Cessation Clinic is available to anyone, including the public and M. D. Anderson patients, family, friends, and staff. It is located in the Cancer Prevention Center, which also provides head-to-toe cancer screening and early detection examinations, recommended annually for all adults.

"Because most smokers want to stop, their stay here—as patient, family member, visitor, or staff—may present a critical, teachable moment for quitting smoking," says M. D. Anderson's Vice President for Cancer Prevention Bernard Levin, M.D.

In the Tobacco Cessation Clinic, Berry meets individually with anyone interested in quitting smoking or smokeless tobacco.

"Together we devise a cessation and relapse prevention plan that can include nicotine replacement—which can include the patch, gum, inhaler, or nasal spray—antidepressant medication, and individual or group counseling," Berry says. People can complete a cessation program within seven or eight weeks.

For many people, these programs make the difference between quitting tobacco for a while and quitting for good.

"Through counseling, individuals can learn to identify situations where they feel the urge to light up, and to develop new responses that don't include cigarettes or smokeless tobacco," says Therese Bevers, M.D., medical director of M. D. Anderson's Cancer Prevention Center.

The predominant risk factor for developing lung cancer is cigarette smoking. Other risk factors include exposure to second-hand smoke, arsenic, radon, and asbestos.

"Preventing lung cancer through tobacco cessation is crucial to reducing the numbers of people developing the disease. Lung cancer is very difficult to detect until its advanced stages because early symptoms often appear as complaints associated with allergies or the common cold," Dr. Levin says.

Treatment includes surgery, radiotherapy, and chemotherapy, depending on the type and stage of the cancer. The five-year survival rate for all stages of lung cancer is only 14%. Although survival rates approach 49% if detected early enough, only 15% of lung cancers are discovered at this early stage.

"Tobacco use is not simply a habit, but an addiction," says Paul Gincipini, Ph.D., a nicotine researcher in the Department of Behavioral Science. Treatment of nicotine dependence may require the same type of behavioral, societal, and pharmacologic strategies used in breaking addiction to other abused substances, such as alcohol and illegal drugs, he says.

Because of tobacco's addictive power, prevention researchers are continually investigating new methods to help smokers break the cigarette habit. One innovative study involves use of a lightweight, hand-held computer that delivers smoking cessation messages.

"Anyone trying to quit can carry around this wallet-size device. It fits easily into a shirt pocket or purse," says principal investigator David Wetter, Ph.D., of the Department of Behavioral Science. Up to 80 messages can be programmed into the computer, which provides them instantly to quitters who request the messages when feeling the urge for a cigarette.

"The menu of messages is tailored to a wide variety of situations where someone may feel the need to smoke. For smokers trying to quit, a number of circumstances may trigger the smoking urge. This can include times when they are relaxing, feeling tired or angry, when having an alcoholic drink, and when they are around other smokers," Dr. Wetter says.

Some of the messages advise taking a break at work, calling a friend who supports the decision to quit, remembering that smoking is not an option, and taking a brisk walk. (For a description of a protocol employing this device, see page 9).

For more information, call the Tobacco Cessation Clinic at the Cancer Prevention Center at (713) 745-8040 or (800) 438 6434. For more information about the palm-size computer, call Dr. Wetter at (713) 745 2681.
Health Care of Cancer Survivors Addressed in New Program

Cancer survivors and their special health care needs are the focus of the new Life After Cancer Care program at The University of Texas M. D. Anderson Cancer Center.

"Cancer survivors aren't like people who've had an appendectomy," said Rena V. Sellin, M.D., medical director of the program. "In order to cure people, we're using aggressive, complex treatments. We're superimposing one intervention on another."

Such treatments, while making cancer survival a reality for more and more patients, can have unwanted side effects that may become apparent many years later. These late effects, along with survivors' increased risk of a second malignancy, must be kept in mind and carefully anticipated. Such vigilance ensures that if problems occur, therapy can be instituted promptly. Because long-term follow-up programs are integrated into care of all patients treated at M. D. Anderson, the Life After Cancer Care clinic is devoted to survivors not originally treated at M. D. Anderson.

Dr. Sellin said the list of possible late effects is long. "A two-year-old irradiated at the hip may have orthopedic problems at 15 years. A breast cancer survivor who received Adriamycin has an increased risk of heart damage—and the risk is greater if she received radiotherapy as well," she explained. Many different physical and endocrine sequelae—lymphedema and other physiological problems—can follow.

"In addition," said Dr. Sellin, "there are situations in which standard interventions are contraindicated." Estrogen replacement therapy, for example, which is standard care for many postmenopausal women, is contraindicated in breast cancer survivors because breast cancer is considered a hormonally responsive disease.

Caring for cancer survivors, then, requires knowledge of the possible long-term effects of the cancer and cancer treatment in addition to an understanding of the routine screening and interventions indicated in the general population. This can be a tall order.

"When cancer survivors go back to their primary care physician, they bring some very specialized needs that are outside the expertise of many family physicians," said Dr. Sellin.

"When new late effects or health sequelae and associations are identified, the papers describing such findings and recommendations are published in the oncology journals, not in the primary practice journals," Dr. Sellin pointed out. She offered the example of recent studies showing that female survivors of Hodgkin's disease have an increased risk of breast cancer—a finding with implications for mammography screening. These results were published in Cancer and the Journal of Clinical Oncology. "It can take a while for such information to be disseminated to the family practice physician," she said.

"In our current health system, we have, on one side, the oncologists, who have expertise in the treatment of cancer. Once the cancer is cured, the patient no longer needs 'treatment,' and after a period of time, the oncologist no longer follows the patient. The cancer survivor, then, returns to the care of the primary care physician, who, on the other side, has expertise about anticipating and treating general health problems but may not know what to look for in individuals with complex histories of cancer and cancer treatment."

"I see a lot of people with unique hormonal problems after their treatment," said Dr. Sellin, who is an endocrinologist. "I thought over the
years, wouldn't it make sense to create a clinic focusing specifically on cancer survivors and the problems that they may experience because of their cancer experience?"

She cites the advantage of being at M. D. Anderson. "We work in an environment where we continually keep ourselves up-to-date with state-of-the-art oncology. We always follow our own patients long-term, and we are familiar with treatment sequelae. We could provide a place for people who have been treated for cancer anywhere," she said.

One of the first cancer survivors to take advantage of the Life After Cancer Care program was

"I had an old-fashioned Halsted mastectomy," recalled. "They weren't doing lumpectomies then. There was no choice in those days—if your biopsy was malignant, you signed a paper saying you would have a total mastectomy." Her cancer recurred four years later in the form of a single lung metastasis, which was surgically removed. Since then, she has been cancer free.

When experienced the symptoms of menopause, her gynecologist and her internist both said it would probably be safe to take estrogen, but decided against it. "I was scared," she remembers. "Everything I read said that people who had had breast cancer should not have estrogen."

managed to weather menopause without the aid of hormonal therapy, but as time went on, she became increasingly troubled by a related problem—loss of bladder control. In January 1997, she underwent bladder suspension surgery to correct the problem, but the surgery was not effective. Her gynecologist then proposed another possible solution—Estring, an estradiol-releasing silicone vaginal ring—but he would not prescribe it until she first saw an oncologist. The oncologist advised against Estring.

"He told me, 'Don't rock the boat. You've done too well. You've been a long-term survivor,'" recalls.

When mentioned her concerns to a friend with breast cancer, the friend suggested that go in for evaluation at the Life After Cancer Care program. After some tests, Dr. Sellin prescribed Estring.

"It's changed my life," said whose life was sometimes dominated by the need to find a rest room as often as every 10 minutes. "I was stopping my car every few minutes—I couldn't get anything done," she said. "Now I'm not normal, but it's every four hours."

"It's changed my life."

Patient, Life After Cancer Care

The aim of Life After Cancer Care is to create a program "that thinks only of survivors' issues—not cancer," according to the program's medical director, Dr. Rena V. Sellin.

undergoes frequent blood tests to measure her blood estrogen level to help monitor the safety of the Estring. "Whether I can continue to use Estring, we don't know," said. "But as long as there's no increase in the blood estrogen level, it's okay to use it."

Life After Cancer Care is tailored to the individual patient. "Survivors don't have to stay here for interventions. They can come in for a consultation, and recommendations can be provided for their primary care physician," said Dr. Sellin. If diagnostic or therapeutic interventions are identified, they can often be done by the primary care physician. If specialized care is needed that requires the services of the cancer center, patients can be referred to the appropriate specialist at M. D. Anderson.

Staffed by M. D. Anderson faculty and advanced nurse practitioners, the Life After Cancer Care program is set aside exclusively for cancer survivors. This way survivors "go to a place that thinks only of survivors' issues—not cancer," said Dr. Sellin. "There's a different mind-set from an oncology clinic."

For more information about the Life After Cancer Care program, contact Dr. Sellin at (713) 792-2840 or the M. D. Anderson Information Line at (800) 392-1611 or (713) 792-6161.
Surgical Techniques Offer Hope for Those With Lung Cancer

Garrett L. Walsh, M.D.
Associate Professor, Department of Thoracic and Cardiovascular Surgery

The overall survival of patients with lung cancer has changed little over the past three decades. Less than one of seven patients is alive beyond five years. Because of these dismal results, pessimism often prevails, not only in the minds of the patients and their families but often in the hearts of their attending physicians once the diagnosis of bronchogenic cancer is confirmed.

In the Thoracic Center, we are a group of six chest surgeons attempting to improve these statistics. As surgery with complete resection remains a patient’s best hope for cure, we have adopted a much more aggressive surgical approach to tumors that are often deemed inoperable at other institutions. Cardiovascular techniques are employed for resecting and grafting major vessels should they be invaded by the tumor. Through close collaboration with our neurosurgical and orthopedic colleagues, we have developed techniques that permit en bloc resections and reconstruction of the vertebral bodies for lung cancers that invade the spinal column, locations historically considered untouchable. Through detailed preoperative testing, we have redefined the lower physiologic limits for patients often considered medically inoperable. Many patients whose advanced emphysema or cardiac disease made surgical intervention be considered too risky have safely recovered from curative resections utilizing pulmonary-sparing techniques and close postoperative monitoring in our intensive care and step-down telemetry units.

Neoadjuvant chemotherapy protocols hold promise for locally advanced tumors that can be reduced to facilitate subsequent operations.

In patients who present with advanced stage IV disease, we have many outpatient surgical techniques that can dramatically improve their quality of life. These include a variety of endoscopic procedures, including performing laser resections to reestablish an airway, inserting endoluminal stents to combat tumors that extrinsically compress the airway, and placing brachytherapy catheters for high-dose radiation therapy.

We were the first in Texas to utilize photodynamic therapy for endobronchial tumors and the first in the world to utilize gene therapy to treat patients with lung cancer. We have greater experience than most groups in the world in outpatient management of malignant pleural effusions utilizing the Denver Pleura catheter, a method that avoids hospital admission and prolonged chest tube drainage.

Through a multidisciplinary approach, we are working hard to shine some optimism on a miserable illness that kills more men and women than any other malignancy. In the Thoracic Center, we welcome the opportunity to evaluate any patient, regardless of stage of disease or medical condition.