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Steve Jobs's cancer

Pancreatic neuroendocrine tumors are becoming more common (the bad news) and also more treatable (the good news).

Pancreatic cancer is a dreaded and especially deadly type of cancer. About 44,000 Americans will be diagnosed with pancreatic cancer this year, accounting for approximately 3% of all cancer diagnoses. Unless some dramatic breakthroughs in treatment occur, fewer than 3,000 will be alive in five years.

Steve Jobs fared better than many with pancreatic cancer. The charismatic cofounder of Apple died on Oct. 5, 2011, almost exactly eight years after his cancer was discovered incidentally on a CT scan of his kidneys (the pancreas is near the left kidney). According to the best-selling biography of Jobs that was published shortly after his death, his urologist had urged him to get the scan because of kidney stones he'd had several years earlier.

But some cancer specialists would say Jobs didn't have pancreatic cancer at all—at least not in the way it is usually described. He had a rare form of cancer called a neuroendocrine tumor. They do occur in the pancreas, but two-thirds of neuroendocrine tumors develop elsewhere in the body. Neuroendocrine tumors and the kind of cancer that typically affects the pancreas arise from different types of cells, have different symptoms, and are treated differently. People can lead relatively normal lives for several years with pancreatic neuroendocrine tumors, even if they've metastasized outside the pancreas. Only several thousand cases are diagnosed each year in the United States, although the number has been increasing.

The FDA approved two new drugs for pancreatic neuroendocrine tumors last year, sunitinib (Sutent) and everolimus (Afinitor), which disrupt molecular-level signaling within cancerous cells and work in a much more targeted way than conventional chemotherapy.

Cancer specialists see sunitinib, everolimus, and drugs like them as the new wave of cancer therapy. Sunitinib and everolimus are not mentioned by name in the Jobs biography, but molecular targeted therapy is, so it's a reasonable guess that he might have taken one of those drugs near the end of his life.

A gland in the middle of things

Oblong and tapered at one end, the pancreas invites creaturely comparisons: a small eyeless squid, perhaps, with neither long tentacles in front nor a fin in back. The animal imagery is encouraged by the anatomical division into a head, body, and tail.

Part of the reason pancreatic cancer is so perilous is that the pancreas is so close and interconnected to many other structures. Branches of major arteries and veins serve the organ. The head looks like it is nuzzling the small intestine and is grooved to accommodate the common bile duct that connects the liver to the small intestine. The body lies up against the aorta, and the tail looks like it's invading the personal space of the spleen and the left kidney.

Functionally, the pancreas is a gland—a body part that secretes. But it's an unusual, dual-purpose gland, producing digestive fluids and enzymes that are secreted into the small intestine and insulin and other hormones that are secreted into the bloodstream.

Dr. Matthew H. Kulke, a physician at Harvard-affiliated Dana-Farber Cancer Institute in Boston who specializes in pancreatic neuroendocrine tumors, explained in an interview with the *Health Letter* that pancreatic cancer has traditionally been viewed in this context, with the common type coming ▸▸

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from the cells that produce the digestive juices, and neuroendocrine tumors arising from the islet cells responsible for insulin and other hormones. This is still the dominant view, although Dr. Kulke said the evidence is shifting, and both types may originate from stem cells.

No known risk factors

Smoking, diabetes, and inflammation of the pancreas (pancreatitis) have been implicated as risk factors for the more common type of pancreatic cancer. Nothing similar has been identified for pancreatic neuroendocrine tumors. Some cases are probably caused by inherited genes and, in particular, mutations in a tumor suppressor gene called menin. But the evidence so far is that genetic inheritance accounts for only a small percentage (perhaps 5%) of cases.

The reasons for the increasing number of cases of pancreatic neuroendocrine cancer are difficult to pin down. A definitive diagnosis requires a biopsy. In the past, biopsies weren't done as often as they are now, so some neuroendocrine tumors were probably lumped in with other pancreatic cancers.

The incidental finding on a CT scan, as experienced by Jobs, has become increasingly common (of all cancers, not just pancreatic neuroendocrine tumors), so more detection in this age of high-resolution medical imaging may be the reason for some of the increase. But the possibility that there's been a true increase in the number of these types of tumors can't be ruled out, either.

Typing cancer

Cancer is identified not only by its location but by the type of cells it originated from—its lineage, so to speak. Sarcomas, for example, come from bone, muscle, and various kinds of connective tissue. Carcinomas, the most common type of cancer, arise from epithelial cells that line various parts of the body.

Most pancreatic cancer is adenocarcinoma, cancer that originates from ductal tissue. Neuroendocrine tumors affect cells that produce hormones. The pancreas is a common site for neuroendocrine tumors, but they also develop in the small intestine, appendix, and other parts of the body, where they are known as carcinoid tumors.

Removing the tumor

Pancreatic neuroendocrine cancer can be removed surgically. Usually enough of the pancreas and insulin-producing islet cells are left behind so the patient doesn't become diabetic.

Large tumors may indicate that the cancer has spread outside the pancreas, but that isn't always the case. "We've recommended resection of large, 10-centimeter tumors, with no metastasis, and the patients have done great," Dr. Kulke told us. Generally speaking, surgery is not done if the cancer has already metastasized outside the pancreas, because the procedure would probably do little to alter the course of the disease.

Much has been made about Jobs delaying surgery for nine months as he tried alternative treatments and a strict vegan diet (Jobs was on and off vegan and fruit diets throughout his adult life). Any judgment about whether the delay made a significant difference would require more detailed knowledge of his case. It is possible that the cancer had already spread, perhaps undetected, outside his pancreas by the time Jobs was diagnosed, in which case the timing of the surgery would have been of little consequence.

Taming hormones

Between 10% and 30% of pancreatic neuroendocrine tumors result in excess secretion of insulin or, depending on the particular type of islet cells involved, other hormones. If too much insulin is pumped out, blood sugar levels can plummet. Extra gastrin, a hormone that stimulates the stomach, can lead to stomach ulcers. Surplus glucagon can make blood sugar levels go up. In the past, people with pancreatic neuroendocrine tumors died from these hormonal excesses, not the cancer itself. Now a class

of medications called somatostatin analogs can be used to effectively control hormone secretion. Somatostatin analogs may also slow the growth of the tumors themselves.

Treating tumors that spread to the liver

When pancreatic neuroendocrine tumors spread, the first place they tend to go to is the liver. Depending on the location and the extent of the cancer, it can be removed surgically. If surgery isn't possible, some patients get a procedure called hepatic arterial embolization, which blocks one of the main arteries supplying the liver. The cancer doesn't go away, but starved of blood, it may shrink.

After his cancer spread to his liver, Jobs got a liver transplant in 2009. Dr. Kulke described liver transplants for pancreatic neuroendocrine tumor patients as "highly investigational." A transplant doesn't preclude the cancer from recurring, either in the new liver or elsewhere in the body, he pointed out. And, of course, sadly, Jobs's cancer did come back. According to the biography, Jobs's diseased liver was full of cancer when it was removed, which meant it was likely the cancer had already spread outside the pancreas and the liver. The biography also says the doctors saw suggestive spots on his peritoneum, the membrane that lines the abdominal cavity.

'Think different' cancer treatment

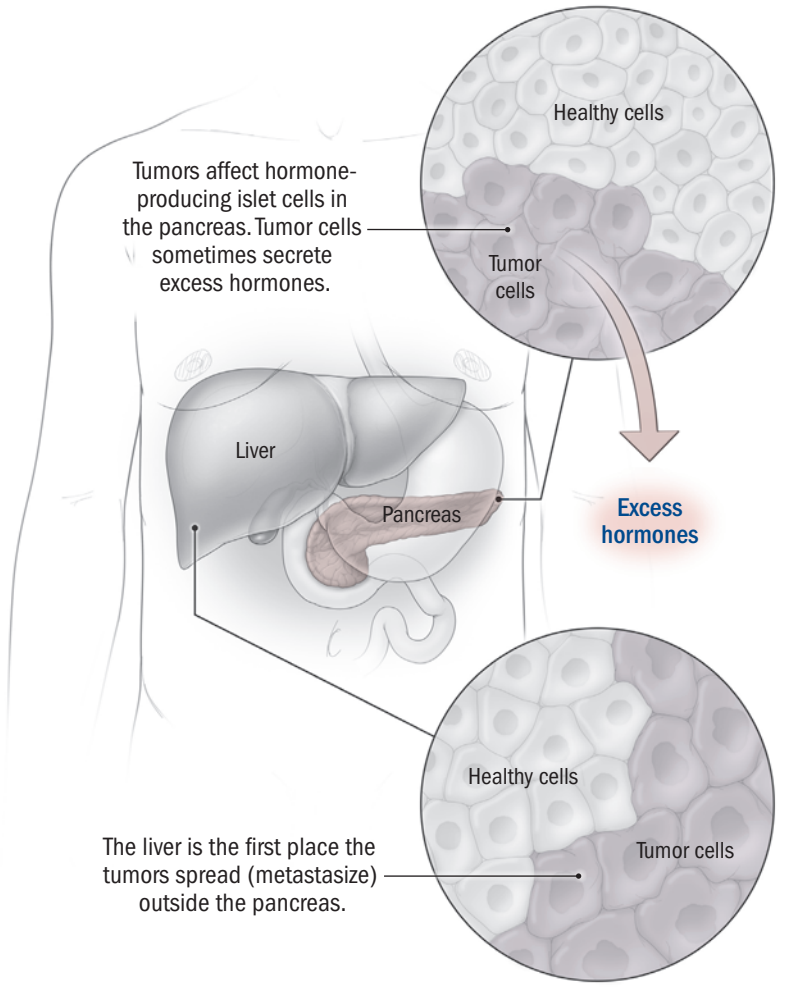
Conventional chemotherapy, which attacks cancer by disrupting and killing off rapidly dividing cells, can be used to treat pancreatic neuroendocrine cancer after it has metastasized. It extends how long people live, but it doesn't cure the cancer, and the usual chemotherapy side effects (nausea, hair loss, possible kidney problems) from one of the drugs used to treat pancreatic neuroendocrine cancer, streptozocin, may be especially harsh.

Dr. Kulke, who led early studies of sunitinib, said it and everolimus are exciting new alternatives to conventional chemotherapy that has been the mainstay for over 20 years. Like imatinib (Gleevec), the first of this new wave of targeted drugs, sunitinib inhibits tyrosine kinase, an enzyme critical to a complex chain of chemical events—a "signaling pathway"—that results in the runaway proliferation and spread of cancer cells. Everolimus inhibits a different enzyme, mTOR, and a different pathway, but the basic concept of homing in on a molecular-level target specific to cancer cells is the same. Jobs, who was obsessed with design, perhaps appreciated the more precise design of these drugs.

The results with sunitinib and everolimus for pancreatic neuroendocrine cancer haven't been nearly as dramatic as those for imatinib and chronic myelogenous leukemia (CML), a rare blood cancer. But they have been shown to cut the growth of metastatic pancreatic neuroendocrine cancer in half. Sunitinib and everolimus have side effects, which include high blood pressure and a drop in infection-fighting white blood cells, but over all, they're less serious than those from conventional chemotherapy.

Unusual cancers like pancreatic neuroendocrine cancer often put patients (and their doctors) in uncharted territory with few, if any, proven treatments. Patients and their doctors try chemotherapy regimens used for more common cancers and hope for the best. The tables may turn in this new era of targeted drugs, said Dr. Kulke, with unusual cancers becoming more treatable, and lessons learned treating the rare cancers applied and adapted to the more common ones.

Pancreatic neuroendocrine tumors



What is it about coffee?

Research is showing benefits for everything from depression to liver disease. Is it just the caffeine?

Remember when people (and their doctors) used to worry that coffee would harm their hearts, give them ulcers, and make them overly nervous?

In excess, coffee, and more particularly, caffeine, can cause problems. But the fretting about two or three cups a day, or even more, is fading as study results suggestive of health benefits from coffee keep on coming in. Just in the past year, researchers have reported findings that coffee drinking is associated with a lower risk of depression among women, a lower risk of lethal prostate cancer among men, and a lower risk of stroke among men and women. Go back a little further, and you'll come across reports of *possible* (it's not a done deal) protective effects against everything from Parkinson's disease to diabetes to some types of cancer (see sidebar on the next page).

Caffeine has been studied more than any other ingredient in coffee, and it tends to get credit if the body part benefited is the brain. But coffee contains literally a thousand different substances, and some of the lesser lights are thought to be responsible for healthful effects in other parts of the body. Some studies show caffeinated and decaffeinated coffee as having the same effect, which suggests that something else in coffee is involved.

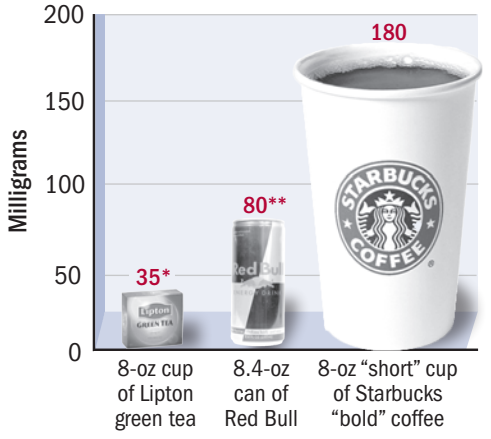
It gets complicated, though. Caffeine and some of these other substances in coffee seem to have their good and bad sides, and coffee's overall effect may depend on how much they cancel each other out.

Caffeine: Good for the brain, bad for other parts?

Caffeine is the most commonly consumed psychoactive drug in the world, and some of its behavioral effects (such as arousal) may resemble those produced by cocaine, amphetamines, and other stimulants. Coffee consumption accounts for about 75% of the adult intake of caffeine in the United States, although that might be changing among younger adults with the growing popularity of energy drinks.

The caffeine content of coffee varies greatly, depending on the beans, how they're roasted, and other factors, but the average for an 8-ounce cup is about 100 milligrams (mg). Tea has about half as much caffeine as coffee. Decaffeinated coffee has some caffeine, but the 2 to 4 mg in an 8-ounce cup is a smidgen compared with the caffeinated version. The lethal dose of caffeine is about 10 grams, which is equivalent to the amount of caffeine in 100 cups of coffee.

Caffeine content



*35 mg presumes a single tea bag steeped in 8-ounce cup
**Per 8.4-ounce can

Caffeine gets absorbed in the stomach and small intestine and then distributed throughout the body, including the brain. The amount circulating in the blood peaks 30 to 45 minutes after it's ingested and only small amounts are around eight to 10 hours later. In between, the amount circulating declines as caffeine gets metabolized in the liver.

Tobacco and marijuana accelerate caffeine metabolism, which reduces the time caffeine circulates in the body. Oral contraceptives slow it down, so they have the opposite effect. Researchers have identified genes that influence a person's natural risk of caffeine metabolism, which might explain why some people are exquisitely sensitive to caffeine while others are not.

Caffeine probably has multiple targets in the brain, but the main one seems to be adenosine receptors. Adenosine is a brain chemical that dampens brain activity. By hogging adenosine's receptors, caffeine sets off a chain of events that affects the activity of dopamine, another important brain chemical, and the areas of the brain involved in arousal, pleasure, and thinking. A part of the brain affected by Parkinson's disease, called the striatum, has many adenosine receptors; by docking on them, caffeine seems to have some protective effects.

Outside the brain, caffeine can be a performance enhancer, boosting the strength of muscle contraction and offsetting some of the physiological and psychological effects of physical exertion. But, especially in the short term, it also has negative effects, which include raising blood pressure, making arteries stiffer, and increasing levels of homocysteine, insulin, and possibly cholesterol. Habitual use may cause some of these effects to wear off. For some conditions, though, coffee may have some benefit despite, rather than because of, caffeine.

Cafestol and kahweol: Filtering out cholesterol boosters

Coffee drinkers concerned about cholesterol weren't happy about some early study results showing that coffee seems to increase cholesterol levels, and "bad" LDL cholesterol levels in particular. But upon closer inspection, the bad news turned out to be not so bad, because the cholesterol-raising effect seems to be limited to coffee that hasn't been filtered, which includes Turkish coffee, coffee brewed in a French press, and the boiled coffee consumed in Scandinavia.

The cholesterol-raising ingredients in coffee are oily substances called diterpenes, and the two main types in coffee are cafestol (pronounced CAF-es-tol) and kahweol (pronounced KAH-we-awl). They are present either as oily droplets or in the grounds floating in the coffee. But a paper filter traps most of the cafestol and kahweol, so coffee that's been filtered probably has little, if any, effect on cholesterol levels.

The best evidence is for paper filters, but an interesting study published last year showed that filtering methods used in Singapore (the so-called sock method, which uses a cotton-nylon cloth) and India (metal mesh) were also effective at trapping cafestol.

Espresso contains more cafestol and kahweol than paper-filtered coffee, but because it is consumed in smaller amounts, it may not have much of an effect on people's LDL level.

There is a twist to this aspect of the coffee story, because cafestol and kahweol may also have some health benefits that are lost when they're filtered out. The research is in the preliminary stages, but cafestol and kahweol could have some anticancer effects and be good for the liver.

Chlorogenic acid and other antioxidants

Explanations for the association between coffee consumption and lower rates of heart disease and diabetes often point to chlorogenic acid and other obscure antioxidant substances as the responsible parties. Antioxidants are substances that sop up reactive molecules before they have a chance to harm sensitive tissue like the lining of blood vessels. Chlorogenic acid was probably the main antioxidant in your cup of coffee this morning. Some experiments have shown that it may also inhibit absorption of glucose in the digestive system and even out insulin levels.

Chlorogenic acid might be another coffee ingredient with a split personality. Along with caffeine, it seems to push up levels of homocysteine, an amino acid that has been associated with artery-clogging atherosclerosis.

Vitamins and minerals

Coffee isn't a great source of vitamins and minerals, but as a plant-based drink, it contains some, and a few that we should be getting more of.

Let's start with magnesium. A cup of coffee contains about 7 mg, which is a drop in the daily-requirement bucket (420 mg for men, 320 mg for women). But because we don't eat enough fruit, vegetables, and whole grains, the average American's intake falls about 100 mg short of the daily goal. A cup of coffee or two can help close that gap a little bit.

Potassium can offset some of the negative consequences of sodium. At about 116 mg per cup, coffee's contribution toward the 4,700 mg of the potassium that we're supposed to get daily is a widow's mite, but it's something. A cup of coffee also has small amounts of niacin (0.5 mg) and choline (6.2 mg).

A health drink? Not quite.

It is one thing to say that coffee may be good for you; it's another to say it's *so* good for you that drinking it should be recommended. And we're not there yet.

All of the favorable studies and all of the seemingly healthful ingredients in coffee are good news for coffee drinkers. They can relax and enjoy their habit. And people who don't drink coffee can find plenty of other things to do to help keep themselves healthy.

Coffee: A disease-by-disease report card

Alzheimer's disease	Human and animal studies show hints of protection. Some preliminary evidence suggests activity against beta-amyloid plaque that may have a causative role in Alzheimer's.
Cancer	Studies suggest a lower risk for some cancers (endometrial, aggressive prostate, estrogen-negative breast), but not others (esophageal). Antioxidant and anti-inflammatory substances could be responsible for possible anticancer activity.
Diabetes	Effects on insulin and blood sugar levels that would promote diabetes seem to be temporary. Regular use is associated with lower risk, and high intake (3–6 cups a day) seems to have a greater effect. Protection may come from increases in the hormone adiponectin and other factors that affect insulin and blood sugar levels.
Heart attack	Coffee drinking increases some factors (homocysteine) associated with higher risk. But moderate consumption (1–3 cups a day) has been linked to a small decrease in risk. The evidence for a possible protective effect is stronger for women.
Liver disease	Coffee drinking is associated with lower levels of enzymes that indicate liver damage and inflammation. Coffee may improve response to some treatments for hepatitis C. Findings suggest some protection against liver cancer. Cafestol and kahweol, substances found in unfiltered coffee, may be responsible for liver benefits.
Parkinson's disease	Studies show a moderate (25%) decrease in risk for coffee drinkers. The effect is less in women. Research has found evidence of activity in the part of the brain affected by Parkinson's.
Stroke	Moderate consumption (3–4 cups a day) is associated with lower risk. But chance of a stroke may increase immediately after intake, particularly among infrequent consumers.

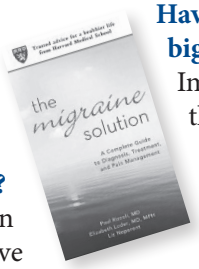
Talking about migraine

Dr. Paul B. Rizzoli is director of the John R. Graham Headache Center at Faulkner Hospital in Boston. He is co-author of The Migraine Solution: A Complete Guide to Diagnosis, Treatment, and Pain Management, *a Harvard Health Publications/St. Martin's Press book being published this month.*

What is a migraine headache?

Migraine can be defined as a limiting headache—a headache that stops you from functioning. The pain is not a mild, insignificant thing you can ignore; you must actively decide what to do about it. Nausea is also a common symptom.

More and more it seems like migraine is a separate illness. In the future, it's likely that we'll be able to define migraine by its distinct genetic pattern.



Where does the pain come from?

We think that migraine "lives" in the brain. The brain doesn't have pain receptors, but it processes pain signals from other parts of the body. It's the pain processing networks, or centers, in the brain that are overly reactive or dysfunctional in migraine.

Isn't there a theory that the pain comes from the dilation—widening—of blood vessels in the brain?

That was the dominant theory in the '60s. But much of the evidence now is that blood vessel constriction and dilation is an epiphenomenon—something that accompanies the pain from migraine but doesn't cause it.

Where do triggers fit in?

The notion of triggers is central to the diagnosis of migraine. We look for patterns of reactivity and for events or circumstances that set off individual headaches. The problem is that even when you identify triggers, there's frequently not a lot you can do about them. You can't control weather changes, for example.

I think triggers have often been overemphasized in some of the self-help approaches to migraine. Advice on managing triggers can suggest a sense of personal control over migraines that often isn't there.

And dietary triggers?

They exist, but I also think that people can drive themselves crazy trying to identify them. We frequently hear patients report that when they are adequately treated, chocolate, alcohol, and other dietary triggers disappear.

Have drugs like Imitrex made a big difference?

Imitrex [sumatriptan] is one of the triptan drugs. The triptans have revolutionized treatment of migraine headaches once they start to occur—what we call abortive treatment. They allow people to take a specific medicine to target a specific condition and often get back to having a fairly normal day.

People also take medication on an ongoing basis to keep the headaches from occurring, don't they?

Yes, we have three major groups of preventive medications that we prescribe: antiseizure medications, blood pressure drugs, and the older tricyclic antidepressants. It is a diverse set of agents, and why they work is not entirely clear, but they seem to reduce headache reactivity—the triggers may still be there, but they fail to set off the migraine event. Botulinum toxin—Botox—injections into various places the head seem to help reduce headache reactivity in some people.

Is there one that you prescribe more than the others?

I have found amitriptyline [Elavil, Endep, others], one of the older tricyclics, to be particularly effective, often at a low dose: 10 milligrams a day compared with the 100- to 150-milligram dose that was used for depression. Sedation and weight gain are side effects. Amitriptyline is long-acting, so I usually recommend that people take it around dinnertime so they don't sleep too late.

Are there any alternative approaches that work?

Complementary and alternative therapies are usually not strong enough to treat a tough migraine problem alone, but they might be helpful for a mild one. And a lot of these treatments are very hard to study in a double-blind fashion.

The technique for which there is the most evidence is biofeedback, but the problem is that biofeedback is not widely available and often isn't covered by insurance. My own personal favorite for patients is yoga, because it is so widely available and affordable, and it probably has other health benefits.

What about supplements?

Headache specialists seem to love to argue about them. Everybody has their favorite combinations. I suppose the ones I like are melatonin, the sleep hormone; coenzyme Q_{10}; and magnesium.

How has your own understanding of migraine evolved over the years?

Certainly our knowledge about migraine has improved. But if I had to pick one thing, it would be my appreciation of just how much of an impact migraines can have on people's lives. It took me 15 to 20 years to really understand what migraine patients are going through and what a huge impediment migraine is on their lives. I've also come to understand that it often takes a lot for people to come in for care. Many patients have some level of shame about their migraines.

Shame? Really?

Shame is a strong word, but I think it's appropriate. They have shame because they think they should be able to handle it on their own. And shame because they have often made an effort to talk to doctors about migraine and have been passed off as complainers.

Try yoga for back pain (but talk to your doctor first)

Two studies published late last year should encourage you to try yoga if you have a bad back. In one study, British researchers compared a 12-week yoga program with usual care provided by Britain's National Health Service and, not surprisingly, yoga proved to be more effective than routine care. In the other study, researchers at the Group Health Cooperative in Seattle compared yoga with "self-care" and exercise classes that were specially designed for the study. The exercise classes included some warm-ups and strength exercises, but most of the time (about 50 minutes) was spent on 15 different stretching exercises targeting the trunk and legs. The study ended in a tie, with yoga and the exercise classes having a similar effect on people's back pain, as measured by self-reported "bothersomeness" and, as in the British study, by the effect on back-related problems with walking, standing, and so on. Self-care finished a distant third.

The Group Health researchers noted that at a purely physical level, the yoga and the stretching classes were pretty similar. In some sense, the study compared yoga with a yoga-like set of stretching exercises.

In the real world, yoga is the more practical choice. A stretching program tailored to the back is going to be hard to find, while virtually every health club and Y offers yoga classes and there are yoga studios everywhere.

Yoga is safe, but if you are getting into it as a treatment, talk it over with your doctor, especially if your problem is back pain. Certain yoga classes (and positions) are going to more suitable than others for people with back pain. In the British study, 5 (3%) of the 156 study volunteers who were randomized to yoga reported that their back pain increased and that the increase was related to yoga. In the Group Health study, 13 (15%) of the 87 yoga class participants reported mild to moderate problems, mainly related to back pain, and one person suffered a herniated disk.

Watch out for medical identity theft

Identity thieves are moving into the health care business in a big way.

A recent survey of doctors, insurers, and pharmacies found that a third of them had caught someone using another person's identity to get health services. But in many cases, the thieves are after billing information so they can make fraudulent claims. In one recent scam, older people were called up and told that they needed to provide their current Medicare number because the federal health care reform law required that they get a new one, which isn't true. The scammers could then use the Medicare numbers to bill the government for services that were never delivered.

The Federal Trade Commission has some suggestions for preventing medical identity theft. They're pretty basic but, at the very least, serve as useful reminders:

- Never give out personal or medical information on the phone or through the mail unless you initiated the contact and are certain you know who you are dealing with.
- Be skeptical of offers of free or sharply discounted services from providers you don't know who ask for your Medicare or health insurance information. Medical identity thieves, posing as insurance company employees and doctors and other health care providers, lure people in with these offers, collect their billing and other information, and then use it to make Medicare and other claims.
- If you're asked to provide insurance or medical information on a website, look for indicators that the site is secure, such as a lock icon on the browser's status bar or a Web address that begins "https" (the *s* stands for secure).

Tea and coffee with your fish?

Fish ranks way up there on the list of healthful foods we should be eating more of. But depending on the species and the water it was harvested from, it comes with a catch, because mercury travels up the food chain and accumulates in fish flesh. Brain and neurological damage to children and developing fetuses is the main risk from methylmercury, the form found in fish, but methylmercury is probably not all that healthy for adults, either.

Canadian researchers may have figured out a way for us to eat our fish without the mercury, too. Their lab experiments have shown that the combined effect of cooking fish (sorry, sushi lovers) and tea or black coffee makes mercury far less likely to be taken up by the body. So a few sips of tea or coffee with your salmon or trout could lower the risk of mercury that you're consuming from causing you harm. It's an intriguing idea, but this is a preliminary finding that needs to be backed up by more research.

Coldhearted is not healthy

April may be the cruelest month, but January is the coldest in many parts of the country. Exposure to cold has a variety of physiological effects that ramp up blood pressure and may make blood more likely to clot. Numerous studies have shown that heart disease deaths and hospitalizations peak during the winter. Others factors may be involved (flu infections, for example) but chilly temperatures almost certainly contribute.

BPH drugs for preventing prostate cancer

Q I take Avodart for my enlarged prostate. But I heard that Avodart increases prostate cancer risk. Is that true? Should I quit taking Avodart?

A You are on the right track about the cancer risk, but it's complicated.

In June 2011, the FDA did, in fact, add a warning to the label of Avodart and other drugs in its class about the possibility of an increased risk of *high-grade* prostate cancer. And I was a member of the advisory committee to the FDA that recommended that Avodart and drugs in its class *not* be approved for prostate cancer prevention—a recommendation the agency followed.

Why would the FDA even be considering approving Avodart for prostate cancer prevention if it's associated with high-grade prostate cancers? Let me explain, starting with a little background.

An enzyme called 5-alpha reductase converts testosterone to another, more potent male hormone called dihydrotestosterone—DHT for short. DHT promotes the growth of prostate gland tissue (and, it just so happens, also activates hair follicles). Avodart—the generic name is dutasteride—inhibits 5-alpha reductase, so it shrinks the prostate gland by lowering DHT levels without affecting testosterone levels. That's why it's prescribed for benign prostatic hyperplasia (BPH), noncancerous growth of the gland that can cause urinary problems.

The other 5-alpha-reductase inhibitors include finasteride (sold under the brand name Proscar, but also available as generic) and Jalyn, a new combination pill. Because of its effect on hair follicles, finasteride is also sold in a low-dose form as Propecia, the baldness drug.

It made sense to test whether the 5-alpha-reductase inhibitors, with their DHT-lowering, prostate-shrinking effects, might lower men's chances of getting prostate cancer. Two large studies were done, one of finasteride and the other of Avodart. And there was good news: relative to a placebo, both drugs reduced the overall prostate cancer risk by 25%. The problem is that the cancers that they prevented were mainly low-grade cancers—cancers that aren't likely to spread—and they resulted in small, but real, increased risk for high-grade tumors. There are many ways to do the math based on these studies, but here's a way that was presented at the FDA advisory committee meeting that puts things in the proper perspective: for every 150 to 200 men taking finasteride or Avodart for prostate cancer prevention, between three and four low-grade cancers would be prevented but one additional high-grade cancer would occur.

The bar needs to be set very high for any drug that men might take to prevent prostate cancer, given the fact that it could potentially be prescribed for millions of men who may never develop the disease in the first place. I think the FDA made the right decision not to approve the 5-alpha-reductase inhibitors for prostate cancer prevention because of the small increased risk of high-grade cancer.

But the risk-benefit balancing act is very different for men like you, who are already taking a 5-alpha-reductase inhibitor for BPH. Avodart and finasteride are very effective for BPH. When BPH isn't effectively treated, it can cause urinary retention—an inability to empty the bladder—that can be serious and very painful. Treating BPH with medication can also help men avoid surgery to treat an enlarged prostate. Ultimately, of course, it's up to the patient, but I think for most men the benefits of these drugs for BPH outweigh the small cancer risk.

That being said, the prostate-specific antigen (PSA) levels of men taking a 5-alpha-reductase inhibitor for BPH should be monitored closely. If PSA levels start to rise in a man who is taking one of these drugs, he should talk to his doctor about possibly having a biopsy to understand what may be causing that increase, because it could be caused by prostate cancer.

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