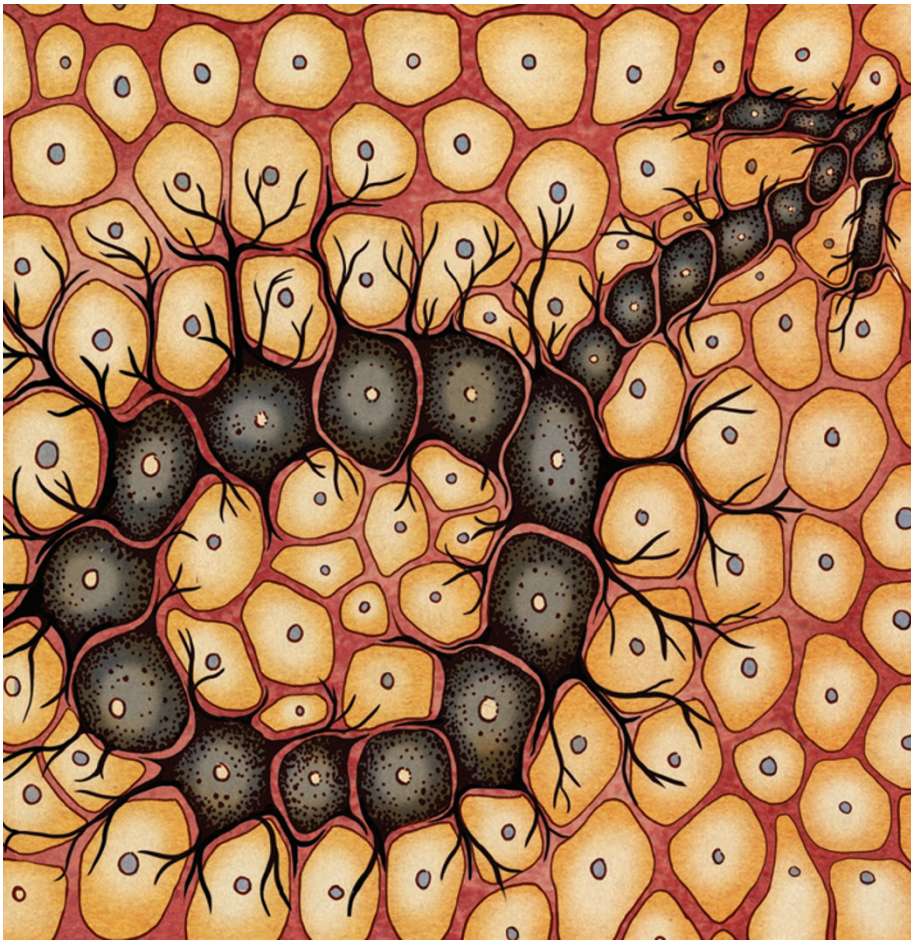


KATIE SCOTT

SEX DIFFERENCES

Luck of the chromosomes

Liver cancer strikes many more men than women — finding out why could lead to new ways of preventing the disease.

BY COURTNEY HUMPHRIES

A multitude of well-studied factors influence a person's susceptibility to cancer — genetic background, chemical exposure, diet and behaviour all contribute. But one factor that seems to play a major part in malignancy has received surprisingly short shrift from scientists: whether someone is male or female.

Some cancers, such as prostate or ovarian cancer, are by their very nature limited to men or women, and others, such as breast cancer, have a known connection to sex hormones. But even cancers with no clear association to sex disproportionately affect males or females for reasons that no one yet fully understands. On balance, men get the worse lot: a sizeable list of cancer types are more common in men than women, as is cancer overall.

The imbalance is especially evident in hepatocellular carcinoma (HCC), the most common liver cancer (see 'Sexual inequality'). It affects twice as many men than women, and seems to be more aggressive in men, too. According to one analysis, women under 55 with HCC have a 17% greater chance of survival than men of the same age (although that difference disappears over the age of 65).

Historically, scant attention has been given to the reasons for this difference in susceptibility. But in the past decade, researchers have begun to uncover tantalizing biological clues: they have identified links among hormones, inflammation and liver-cancer risk that could lead to new approaches for treating or even preventing the disease. In so doing, they may even help to clear up part of the larger mystery of why cancer, in general, afflicts more men than women.

Behaviour is partly to blame: men are more likely than women to drink, for instance, and alcohol use is a major risk factor for liver cancer. But this alone does not explain the disparity: even in rodent models of the disease, males develop more tumours than females. "It's absolutely biological. It's not lifestyle driven," says Arlin Rogers, a liver oncology researcher at the Cummings School of Veterinary Medicine at Tufts University in North Grafton, Massachusetts. "Male mice and rats don't drink more than female mice and rats."

Liver cancer almost always develops as a consequence of long-standing liver injury and inflammation caused by disorders such as hepatitis B (see page S12), hepatitis C, fatty liver disease (see page S8), alcoholism and cirrhosis. Any differences in susceptibility to inflammation between male and female livers could potentially contribute to a difference in cancer rates, says Gyongyi Szabo, a liver-disease researcher at the University of Massachusetts Medical School in Worcester — and multiple factors can amplify one another.

HORMONAL DIFFERENCES

A surprising number of fundamental differences separate male from female livers. A person's sex seems to have broad effects on how the liver develops, and hundreds of genes are expressed differently in men's versus women's livers. Many of these affect metabolism, causing male and female livers to metabolize certain drugs, toxins and carcinogens differently, says David Waxman, a cell biologist at Boston University in Massachusetts. "The liver is perhaps the best example to date of a non-reproductive tissue that shows wide differences between males and females in gene expression in general," he says. Many of these differences are caused by the pattern of growth-hormone release during development — the hormone is released in periodic pulses in males, and more steadily in females.

There are also lifelong differences in hormone levels between men and women, most obviously in levels of the sex hormones oestrogen and testosterone. The androgen receptor, which binds testosterone and other male hormones, has been implicated in liver cancer: this receptor is found in both men and women, but it occurs at higher levels in men.

The clearest evidence for a connection between the androgen receptor and liver cancer comes from male mice infected with hepatitis B virus (HBV) — the most common cause of liver cancer worldwide. In one particularly telling study, researchers genetically engineered mice to have livers that do

not contain the androgen receptor[1]. When they administered a chemical that is known to promote liver cancer, both the male and female mice had a lower incidence of liver tumours than did control mice. (The sex differences, although diminished, were not entirely abolished.) Chawnshang Chang, a cancer researcher at the University of Rochester Medical Center in New York and senior author of the study, notes that the androgen receptor enhances the virus's ability to replicate, and the receptor–virus interaction triggers the expression of genes that are linked to liver cancer.

Chang suggests that one way to interfere with this interaction is to therapeutically block activity of the androgen receptor in the liver. Chang founded AndroScience, based in Solana Beach, California, to develop one such drug, ASC-J9, which he believes could be useful for attacking liver cancer caused by HBV. It recently completed a phase II safety and efficacy trial as a topical acne medication but has not yet been tested as a human cancer treatment.

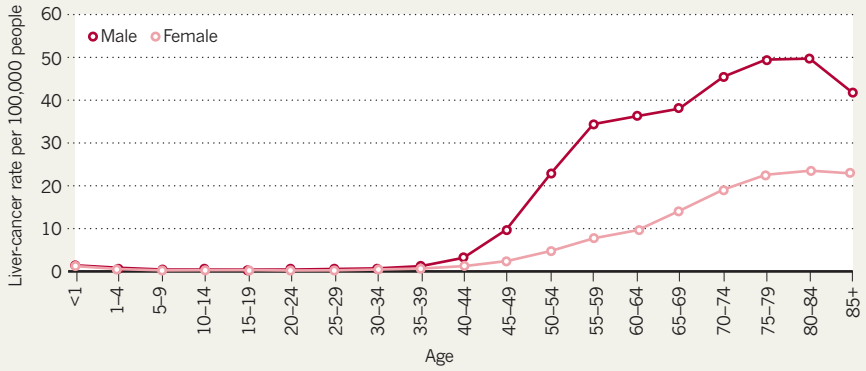
Whereas the androgen receptor seems to promote HBV-associated liver cancer, the oestrogen receptor might have exactly the opposite effect. Some studies have found that, when activated, it dampens viral replication[2], and oestrogen might also protect women by repressing interleukin-6, a protein that is linked to chronic liver inflammation[3]. Because sex hormones are involved in the early or middle stage of liver carcinogenesis, targeting them earlier in the process — for example, when someone has developed a risk factor such as an HBV infection or cirrhosis — might be a way to prevent cancer from developing in the first place, says Pei-Jer Chen, a liver-cancer researcher at National Taiwan University Hospital's Hepatitis Research Center in Taipei.

For a prevention-based hormonal approach to be feasible, Chen says, a drug must target only the liver. The 'chemical castration' hormone therapy given to men with prostate cancer comes with considerable side effects, such as hot flushes and loss of sexual function, and is too severe to give to those deemed at increased risk of liver cancer. Chen's group is currently seeking a drug that targets the liver's androgen pathway. Similarly, an oestrogen-like molecule that worked specifically in the liver could act as a preventative.

Another line of research indicates that, at least in mice, the oestrogen receptor also interacts with the proteins FOXA1 and FOXA2, which help to control various genes in the liver. Klaus Kaestner, a geneticist at the University of Pennsylvania's Perelman School of Medicine in Philadelphia, has shown that both the androgen and oestrogen receptors need FOXA proteins to bind to their molecular targets in liver cells. When mice lacking these proteins were given a carcinogen that causes liver cancer, the male mice had fewer tumours than the male controls and, conversely, the female mice had many more tumours than the female control mice[4].

SEXUAL INEQUALITY

Data from the US National Cancer Institute show the stark difference in liver-cancer rates between men and women. The graph is based on statistics of the institute's Surveillance, Epidemiology, and End Results Program from 18 cancer registries in the United States for 2002–11.



FOXA proteins are too fundamental to the liver's basic function to serve as drug targets, but they could act as biomarkers for liver-cancer risk. Kaestner's team found that women with liver cancer often have genetic variations that stop both the FOXA proteins and the oestrogen receptor from binding to their DNA targets. Genetic variations such as these, Kaestner says, could explain why some people are more susceptible to cancer and could provide a genetic test to identify those most at risk.

THE PROLACTIN EFFECT

Although oestrogen and testosterone have garnered the most attention, another hormone also seems to be involved in liver-cancer risk. Rogers has uncovered an entirely new mechanism that might help to shield women from the disease — one that he believes could be an easy target.

Prolactin, a hormone best known for its role in stimulating milk production, is secreted by the pituitary gland and is present in all vertebrates, male and female. It has hundreds of known biological functions, ranging from regulating water balance to stimulating cell growth. Although it has been well studied in mammalian breast tissue, its role in the liver was not well known.

A surprising number of fundamental differences separate male from female livers.

Rogers found that in cultured mouse liver cells and in living mice, prolactin dampens inflammation, a known precursor to HCC[5]. And mice that had been genetically engineered to lack prolactin had faster-growing tumours than did control mice when exposed to a chemical that promotes liver cancer. To determine whether prolactin had protective potential, Rogers gave male mice a drug called domperidone, which promotes prolactin production. When he later dosed them with the same cancer-promoting chemical, the domperidone-treated mice developed fewer liver tumours.

Domperidone, which blocks the dopamine receptor, is most often used to treat nausea and vomiting; other drugs in its class are widely prescribed for schizophrenia and bipolar disorder. These medications could not be used to treat existing liver cancer, Rogers says, but they offer a way to prevent liver disease from developing into cancer. He is now working with epidemiologists to study whether people with schizophrenia who take these drugs have lower rates of liver cancer. "If we can show an association, then maybe we can sell the idea of intentionally raising prolactin," he says. "We think this might be one approach in high-risk men to reduce risk."

The prolactin study adds yet another twist to a field full of interesting findings but no consensus. "There are a number of different mechanisms that have been implicated, but at the moment no uniform picture has emerged," Waxman says. Independently, the data in each study seem clear and the resulting models solid, he says, "but how do you put it all together?"

Variations between male and female biology go far beyond the most obvious, reproductive differences. Part of the challenge, Waxman says, will be parsing those fundamental differences in tissues such as the liver and then linking them to specific disease mechanisms in males and females. This kind of increased attention to the subtler effects of one's sex could finally begin to explain why inequality prevails in not just cancer but other conditions, too — such as neurological and autoimmune diseases — even if it cannot explain inequality elsewhere. ■

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