Experiment for cancer risk factors

Curiouser and Curiouser

The case-control method used to identify risk factors for cancers relies on prior knowledge about the possible link between the cancer and the risk factors. It is a powerful method as the following two cases show.

Asbestos

In the 1970s, a series of studies identified the risk factor for a rare form of lung cancer called mesothelioma. Case-control studies pinpointed the risk to certain professions: insulation installers, shipyard workers, etc. The statistical analysis pinpointed the risk factor to be “ exposure to asbestos.” Subsequent tort litigation and government oversight precipitated a reduction in occupational exposures to asbestos, reducing the risk of mesothelioma.

Diethylstilbestrol (DES)

Diethylstilbestrol (DES) is a synthetic hormone prescribed to pregnant women in the 1950s to prevent premature deliveries. In 1971, case-control studies found that women with vaginal and uterine cancer had not been exposed to estrogen directly, but their mothers had been. DES, the carcinogen, did not cause cancers to women treated with the drug, but it caused cancers to their daughter who were exposed to the drug in the womb.

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But what if the exposure responsible for the disease is unknown?

A Test for Chemical Carcinogens

Normally, a strain of Salmonella, a bacterial genus, cannot grow on galactose. But when exposed to certain chemicals, it could acquire a gene mutation that enables it to grow on galactose. By counting the number of growth-enabled colonies form, one can quantify the mutation rate in any experiment.

In the late 1960s, Bruce Ames, a bacteriologist at Berkeley, used this technique to test thousands of chemicals on their capacity to create mutations in Salmonella, and created a catalog of mutagens – chemicals that increased the mutation rate. He observed that chemicals that scored as mutagens tended to be carcinogens. Ames didn’t know why mutagens could induce cancer. But he had demonstrated a practical way to find carcinogens.

Hepatitis B virus (HBV)

In the early 1970s, Baruch Blumberg, a biologist in Philadelphia, discovered that a human hepatitis virus can cause chronic inflammation that leads to cancer.

In 1966, Blumberg discovered that individuals carrying the Au antigen (a blood antigen present in several Australian aboriginals) often suffered from chronic hepatitis. Upon further analysis, he found out that au was not a blood antigen but a viral protein floating in the blood. Blumberg’s lab isolated the virus in the early 1970s, and called the virus hepatitis B virus (HBV).

HBV infection caused a broad spectrum of diseases, ranging from acute hepatitis, to chronic cirrhosis in the liver, and to hepatocellular cancer. HBV is a live carcinogen capable of being transmitted from one host to another.

By 1979, Blumberg and his team had found a vaccine for HBV. The vaccine cannot cure the cancer, but it can reduce the incidence of HBV infection.

Helicobacter Pylori (H. Pylori)

In 1979, at the Royal Perth Hospital in Australia, Barry Marshall and Robin Warren wanted to investigate the cause of gastritis. Patients with gastritis are predispose to peptic ulcers and stomach cancer.

Warren believed that gastritis was caused by a yet unknown species of bacteria. But he was ridiculed by mainstream doctors who did not believe any bacteria could live in the stomach.

To prove his point, Marshall and Warren set out to culture the bacteria using brushings from patients with ulcers. But no bacteria grew out. Over a busy Easter weekend in 1982, Marshall had forgotten to examine the culture dish for bacteria for a few days. When he remembered and went to examine them, he found bacteria colonies growing out in the dish. Warren and Marshall called it Helicobacter pylori (H. pylori).

To prove H. Pylori caused gastritis, they inoculated pigs with the bacteria. But the pigs did not get ulcers. In 1984, after failed attempts to infect piglets, Marshall fasted until 10 am and then drank a Petri dish containing cultured H. Pylori, expecting to develop an ulcer. Within a few days, Marshall was violently ill, and diagnosed with gastritis. H. pylori was indisputably the cause of gastritis.

By the late 1980s, several epidemiological studies had linked H. pylori-induced gastritis with stomach cancer. Randomized trials run on the western

coast of Japan showed that antibiotic treatment reduced gastritis and gastric ulcers, and reduced the incidence of gastric cancer. But the it would not cure the cancer once manifested.

A Spider’s Web

If cancer truly transitioned from a precursor lesion – precancer – to its full-blown form slowly, and methodically, then perhaps one could intervene by attacking its precancer, thwarting the progression of the cancer at its earlier stages.

There are two forms of prevention. In primary prevention, you prevent a disease by attacking its cause. For example, stop smoking for lung cancer, or a vaccine against HBV for liver cancer. In secondary prevention, you prevent a disease by screening for its early presymptomatic stage. Pap smear and mammography (discussed below) are examples of secondary preventions.

The Pap Smear – Secondary Prevention for Cervical Cancer

George Papanicolaou, a Greek physician, arrived in New York in 1913. After a few months selling carpets, he found a research position at Cornell University studying the menstrual cycle of guinea pigs. He found that cells shed by the guinea pig cervix could foretell the stages of the menstrual cycle. By the late 1920s, Papanicolaou had extended his technique to human patients. In 1928, he reported that uterine cancer could be diagnosed by means of a vaginal smear. But the importance of his work was not recognized.

Between 1928 and 1950, Papanicolaou delved into his smears ferociously. He became known for his invention of the Papanicolaou test, commonly

known as the Pap smear or Pap test. He knew normal cervix cells change in step-wise fashion in time. Might cancer cells also change in a slow stepwise way from normal to malignant? Could he identify intermediate stages of cancer? A thought occurred to him at a Christmas party in 1950. The real use of the vaginal smear was not to find cancer, but to detect its precursor.

In 1952, Papanicolaou convinced the NCI to launch a clinical trial of secondary prevention using his smearing technique. In the cohort of about 150, 000, 555 women had invasive cervical cancer, while 557 had preinvasive lesions. Early stage preinvasive lesions were curable by a simple surgery. The women with preinvasive lesions had no symptoms. Had they not been tested, they would never have suspected they would develop cervical cancer. The average age of diagnosis of women with preinvasive lesions was about 20 years younger than women with invasive lesions. The Pap smear would detect cervical cancers at an early stage while it is still curable 20 years before they become invasive, giving women a chance to treat it before it evolves into cancer.

Mammograms – Secondary Prevention for Breast Cancer

In 1913, Albert Salomon, a German surgeon, performed a study on 3, 000 mastectomies. He studied the X-rays of the amputated breasts after mastectomies to detect the shadowy outline of cancer. Salomon called his technique mammography. He was able to establish the difference as seen on an X-ray image between cancerous and non-cancerous tumors in the breast. But his studies were interrupted by the Nazis in the mid-1930s. He lived in a concentration camp until 1939 when escaped the camps to Amsterdam and

vanished underground. Mammography, as he called his technique, languished in neglect.

By mid-1960s, with radical surgery being challenged, mammography re-enter X-ray clinics, championed by radiographers such as Robert Egan. Egan’s mammograms could now detect tumors as small as a grain of barley. But would screening women to detect such early tumors save lives?

HIP Trial

In 1963, three men set out to investigate whether screening asymptomatic women using mammography would improve mortality from breast cancer. The three men were Louis Venet, a surgeon; Sam Shapiro, a statistician; and Philip Strax, an internist. They wanted a randomized, prospective trial using mortality as an end point to test mammography.

The trial, launched in December 1963, was kept simple. Women enrollees in the New York Health Insurance Plan (HIP) between 40 and 64 years old were divided into two groups. One group was screened with mammography, and the other not. If a tumor was detected by mammography, the women would be treated according to the conventional treatment available at that time.

In 1971, the initial findings of the trial were remarkable. 62, 000 women participated; about half had been screened by mammography. There had been 31 deaths in the mammography group and 52 deaths in the control group. The percentage reduction in mortality from screening was about 40 percent.

Breast Cancer Detection and Demonstration Project

The positive results of the HIP trial prompted the American Cancer Society to launch a called the Breast Cancer Detection and Demonstration Project (BCDDP). The project, backed by Mary Lasker and virtually every cancer organization in America, intended to screen 250, 000 women in a single year.

Problems with the HIP study

As the BCDDP forged ahead, people were casting doubts over the HIP study. The study had a potential flaw. They had decided to exclude women with prior breast cancer. So they dropped women who had had cancer from each group. But they may have over-corrected: more patients with prior cancer were dropped from the screened group. Critics now charged that the excess mortality in the control group was due to the fact that it was mistakenly overloaded with patients with prior breast cancer.

The Canadian Trial

In Canada, researchers launched their own mammography trial in 1980. But there was a flaw with the study: a woman was randomized after her medical history and examination. The allocations that emerged after the nurse interviews were no longer random. Women with abnormal breast were disproportionately assigned to the screened group. That explains why the results of the CNBSS were markedly negative: The breast cancer mortality of women in the screened group was higher than the unscreened group.

Malmö Mammographic Study

In 1976, 42, 000 women enrolled in the Malmö Mammographic Study. Half of the cohort was screened yearly, and the two groups have been followed closely ever since.

In 1988, the study reported its results. Women older than 55 had benefited from screening, with a reduction in breast cancer mortality by 20 percent. Younger women had no benefit from screening. In 2002, an analysis combining the experience over fifteen years was published in the Lancet. In aggregate, for women aged 55 to 70, mammography screening had resulted in 20 to 30 percent reductions in breast cancer mortality. But for women under 55, the benefit was negligible.