

Special Edition



Dame Valerie Beral, DBE, AC, FRS
Director, Cancer Epidemiology Unit,
University of Oxford
161st Cutter Lecture
The Causes of Breast Cancer
May 6, 2015



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161st Cutter Lecture

Lecturer: Dame Valerie Beral, DBE, AC, FRS

Cutter Lecture on Preventative Medicine

Since 1912, the Cutter Lecture on Preventive Medicine has been one of the most respected presentations, especially in the field of epidemiology. The lectures are administered by the Department of Epidemiology at the Harvard T.H. Chan School of Public Health according to the bequest from John Clarence Cutter, MD (1851 - 1909), a graduate of the Harvard Medical School. He specified that the lectures be delivered in Boston, free of charge to medical professionals and the press. Covering a range of public health topics, the lectures remain dedicated to enhancing the physical and social welfare of the world's population.



Dame Valerie Beral, DBE, AC, FRS

Born in Australia, Dame Valerie studied medicine at Sydney University, graduating in 1969. As the top graduate that year she was awarded the University Gold Medal, the first woman ever to receive this award in medicine. After a few years of clinical work in Australia and New Guinea she moved to the UK and became board certified in internal medicine soon after.

She was fortunate to work for one of the first clinical epidemiologists, Charles Fletcher, who recognised that she was suited to epidemiology and propelled her towards the London School of Hygiene and Tropical Medicine, where she worked for almost 20 years.

In 1988 she moved to Oxford to become the Director of the Cancer Epidemiology Unit, previously directed by Sir Richard Doll. Her major research interests include the role of reproductive, hormonal and infectious agents in cancer and other conditions.

She is principal investigator of the Million Women Study, investigating the effects of a range of women's lifestyle factors on health, with focus initially on the effects of hormone replacement therapy. Since 1991, she has led international collaborative studies of breast, ovarian and endometrial cancers.

Dame Valerie has served on many international committees, including the World Health Organization, the US National Academy of Sciences, and various Australian cancer councils. Until recently, she chaired the UK Department of Health's Advisory Committee on Breast Cancer Screening and is currently a member of the Board of the Medicines and Healthcare Products Regulatory Agency (the UK equivalent of the FDA).

In 2006 she was elected Fellow of the Royal Society (FRS) for scientific contributions to epidemiology. Other honours include being invested as Dame of the British Empire (DBE) and Companion of Australia (AC) for her contributions to science.

She was elected President of the International Epidemiological Association in 2014.

The Causes of Breast Cancer

Breast cancer is a prevalent disease in some of the world's most prosperous nations. Nearly two million women worldwide will be diagnosed with breast cancer by 2030, according to the World Health Organization. That is double the rate of cases in 2000, and most of the increase will be in low- and middle-income developing countries. Today, there is a significantly higher incidence of breast cancer (approximately 6 percent by age 70) among women who live in North America and Western Europe versus rural Africa and Asia (approximately 1 percent), but this socioeconomic disparity is showing signs of seismic shift. Evidence suggests the gap will narrow rapidly. Breast cancer rates are skyrocketing in urban China and Japan, foreshadowing a sobering global impact in the next decade and beyond. In the 161st Cutter Lecture on Preventive Medicine at the Harvard T.H. Chan School of Public Health on May 6, Dame Valerie Beral, Director of Cancer Epidemiology at the University of Oxford, shared what are now believed, for the most part, to be the primary causes of breast cancer. While Beral admitted this is not "rocket science"—the factors are not all that surprising—the road to arriving at these conclusions has been a long journey.

A Hypothesis Proposed Hundreds of Years Ago

For centuries, it was thought that breast cancer occurs when the mammary glands are not used for their natural purposes—breast-feeding. The origins of this idea hark back to Bernardino Ramazzini (1633 -1714), the father of occupational medicine, who suggested breast cancer was a disease associated with nuns due to their celibacy. A century later, in 1842, Italian surgeon Domenico Antonio Rigoni-Stern published research supporting this idea, documenting that 2.7 percent of nuns in Verona, Italy, died from breast cancer between 1760 and 1839, compared to only about 0.4 percent of other women in the same population.

Fast forward to the late 1980s when many medical experts were absolutely certain that the birth control pill, approved for contraceptive use in 1960, caused breast cancer, triggering what Beral calls one of the most powerful controversies in the field of epidemiology. Beral, who was neutral on the topic at the time, convinced the era's leading researchers to allow what later became the Oxford Collaborative Group on Hormonal Factors in Breast Cancer to pool and objectively analyze data they had collected as part of the more than fifty breast cancer studies published to date in the literature. Presenting the Collaborative's findings, says Beral, was one of the most memorable occasions of her life.

Hormones: Heightened Short-Term Risk Diminishes Over Time

Beral and colleagues found that young women taking an oral contraceptive (estrogen plus progestin) faced a 20 percent increased risk of breast cancer while taking the pill and for several years after stopping the regimen. Most importantly, the collective data revealed no long-term increased risk of breast cancer a decade

Special Edition - The 161st Cutter Lecture: Dame Valerie Beral



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later, when these women were in their forties. Despite overwhelming consensus to the contrary, it was concluded that the pill was not, in fact, a significant public health issue. For those who still believed that once exposed to cancer risk, a person carries a lifelong risk, the study's finding of a short-term risk that disappears within ten years was hard to swallow. Nevertheless, the research results were groundbreaking. The findings debunked the theory of the pill as a carcinogen and identified it as a safe contraceptive choice for future generations of women. Today, nearly one billion living women have taken the pill during their reproductive years.

In the late nineties, The Collaborative turned its focus to researching other hormones impacting women's health. The *Million Women Study* followed 1.3 million females, approximately one out of every four women born in the UK between 1930 and 1950, on hormone replacement therapy (HRT). Results were similar to those published regarding the birth control pill. The study produced strong evidence that women taking synthetic ovarian hormones (estrogen only and estrogen plus progestin) face no long-term increased risk for breast cancer. More than 50 million women alive today have relied on HRT to manage the symptoms of menopause.

A study investigating natural hormones (changes in estrogen levels before, during, and after menopause) found that premenopausal women have a 40 percent higher risk of breast cancer than postmenopausal women exactly the same age. This is due to a rapid drop in estrogen levels immediately following the onset of menopause. However, the fact remains that women face a steadily rising risk of breast cancer after age 50.

Ramazzini Was Right

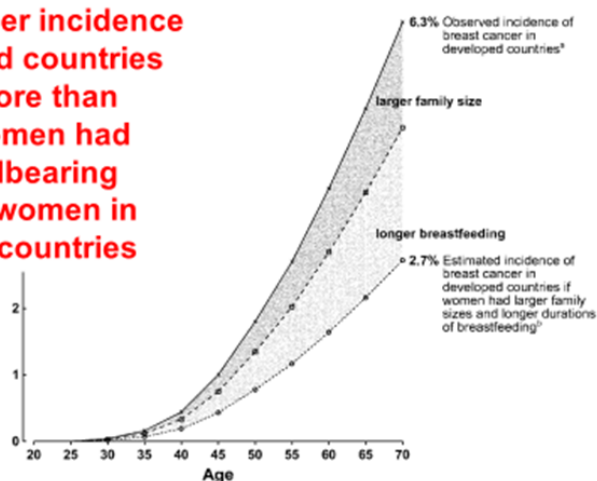
So if neither synthetic nor natural hormones are responsible for causing breast cancer, what can women do to reduce their risk? Turns out Ramazzini was on to something when he declared breast cancer a disease of nuns back in the eighteenth century. Beral says we now know that the risk of breast cancer drops by about 10 percent with every childbirth and another 4 percent for every year of breast-feeding. And, unlike the short-term effects of synthetic birth control pills and HRT, and natural hormonal shifts around the time of menopause, the hormonal changes that occur in pregnancy and lactation deliver persistent, long-term protection against breast cancer.

The significant correlation between number of births and duration of breast-feeding with the incidence of breast cancer helps explain why women in higher-income developed countries like the United States face a six-fold greater risk than women in lower-income developing countries. "Today's western women are a lot like nuns," says Beral, giving birth to fewer children and breast-feeding for much shorter periods of time than women in rural Africa, for example.

Other factors are part of the risk equation. Girls who reach puberty at a younger age and women who are taller, overweight, drink alcohol, or carry susceptible genes are more vulnerable to developing breast cancer. But these factors account for only moderate variations in risk. It is the childbirth and breast-feeding patterns of early adulthood that are ultimately responsible for women facing breast cancer in their post-reproductive years.

Collaborative Group on Hormonal Factors in Breast Cancer

Breast cancer incidence in developed countries would be more than halved if women had similar childbearing patterns to women in developing countries



25-May-15

Lancet 2002

Solid Scientific Work Will Yield Vaccine

Estrogen-blocking drugs like tamoxifen reduce the risk of breast cancer recurrence by up to 50 percent. Such drug therapies are largely responsible for the dramatic reduction in breast cancer deaths in the last two decades. But side effects like menopausal symptoms and a dramatically increased risk of endometrial cancer limit the practicality of this drug as a long-term solution. Since more than half the incidences of breast cancer in developed countries could be eliminated by more births and breast-feeding, it would help if women could just give birth to more babies. But that is nearly as impractical as reducing every woman's estrogen level to zero with high doses of tamoxifen.

Beral says cancer funding bodies and researchers must invest money and make a long-term commitment to understanding and developing a model that reflects specifically what is happening in a woman's body during pregnancy, particularly in the last trimester. We

need to know which and how particular hormones are responsible for permanent changes in breast tissue. Those who figure this out, says Beral, will undoubtedly win the Nobel Prize.

Beral and colleagues believe a solution is attainable. Laborious, systematic, dedicated decades of what may be rather mundane work will lead to a hormonal vaccine that mimics the beneficial breast cell changes that occur during pregnancy and breast-feeding. Only then will countries like the United States and China, bringing fewer children into the world, have the ammunition to battle breast cancer, currently poised to rapidly expand its reach across the globe.



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(Ideas for submission or comments are always welcomed)

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