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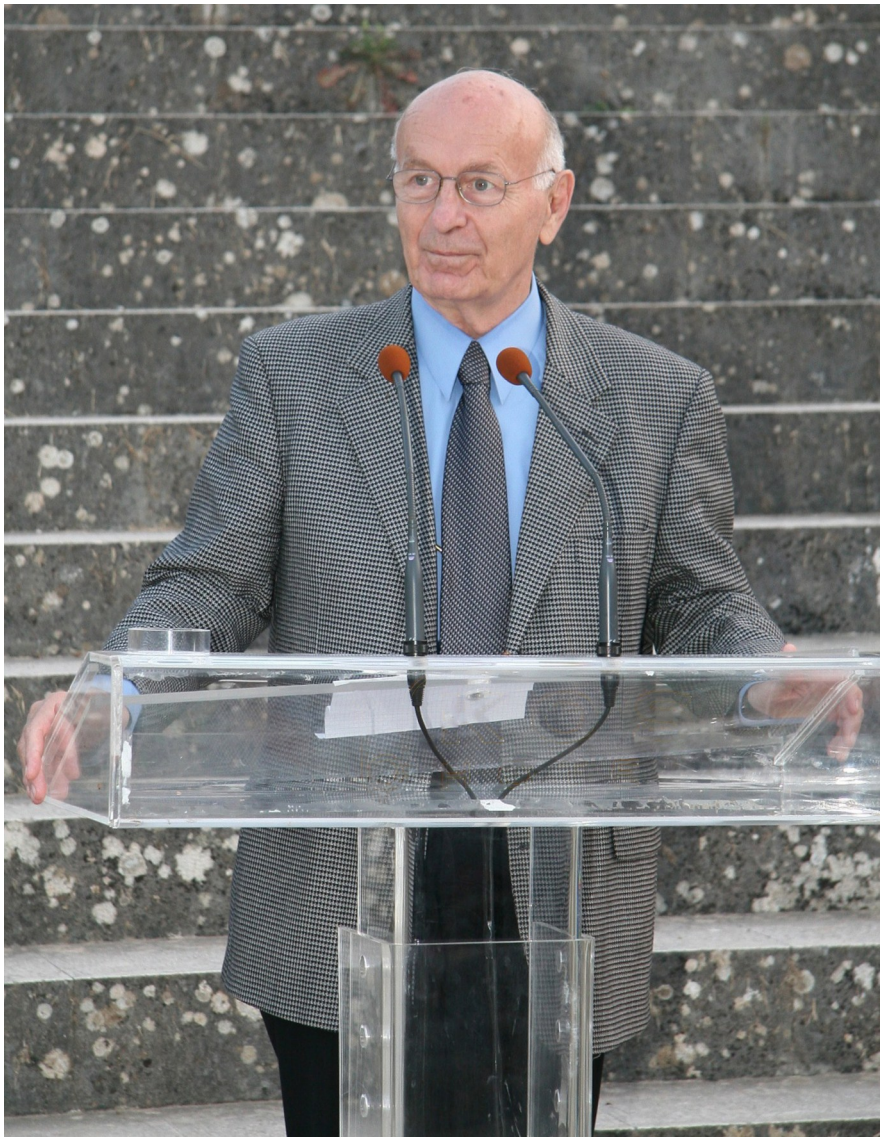
Special Edition



162 Cutter Lecture on Preventive Medicine

Dimitrios Trichopoulos Memorial Symposium

December 2, 2015

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Special Edition

162nd Cutter Lecture

Dimitrios Trichopoulos Memorial Symposium

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.

Dimitrios Trichopoulos

Dimitrios Trichopoulos studied Medicine at the University of Athens and specialized in Internal Medicine, Microbiology, Public Health and Epidemiology at the Universities of Athens, London, Harvard, and Oxford. He has served as Professor and Chairman of the Department of Hygiene and Epidemiology, University of Athens Medical School, Chairman of the Department of Epidemiology, Harvard T.H. Chan School of Public Health, Director of the Harvard Center for Cancer Prevention and as Adjunct Professor of Medical Epidemiology at Karolinska Institutet, Sweden. He is Vincent L. Gregory Professor of Cancer Prevention and Professor of Epidemiology at the Harvard T.H. Chan School of Public Health, and a Regular Member of the Academy of Athens.

Recipient of the "Eleanor Roosevelt" Fellowship; "Cutter Lecturer" at the Harvard T.H. Chan School of Public Health (1982), "Ipsen Lecturer" at the Institute of Social Medicine of Aarhus University (1987) and Cassel Memorial Lecturer, Society for Epidemiologic Research (1999); Member of the Delta Omega Honorary Public Health Society, U.S.A.; Officier de l'Ordre des Palmes Académiques, France; Corresponding Member of the National Academy of Medicine of France and of the Royal Academy of Medicine of Belgium; Chairman of the European Union Health Group during the Greek Presidency (1988) of the European Union; Distinguished Lecturer in the Japan Cancer Research Center (1992) and the National University of Singapore (2007); Honorary Doctor of Medicine, Universities of Uppsala (1994), Thessaly (2007) and Democritus (2009); recipient of a Smoke-Free America Award for demonstrating the role of passive smoking in the development of lung cancer (1996); Commander of Honor of the Greek Republic (1996); Listing by the Editor of the Lancet of a paper by DT among 27 papers deserving to form a Canon for Reading Medicine from antiquity to now (1997); Distinguished Physician, Hellenic Medical Society of New York (1999); Brinker International Award for Breast Cancer Research (2000); Hygeia Award for Contribution to Medicine, New England Hellenic Medical and Dental Society (2001); Grande Covian Award for studies on the Mediterranean diet, Spain (2002); Julius Richmond Award for demonstrating the role of passive smoking in the development of lung cancer (2004); Medal of Honor, International Agency for Research on Cancer, World Health Organization (2007); Honorary Fellow, Royal College of Physicians, London, UK (2008); National Delegate for Greece, Federation of the European Academies of Medicine (2008); Fellow, European Academy of Cancer Sciences (2009); Award of Merit, Harvard T.H. Chan School of Public Health (2009).

Dimitrios Trichopoulos authored or co-authored over 1000 publications (mainly research papers but also books, monographs, reports, reviews, commentaries, etc.), of which more than 800 are listed in international databases. He did extensive original work concerning breast cancer etiology, mainly focusing on the early life origins of this disease. He published the original paper implicating passive smoking in the causation of lung cancer. He contributed to the elucidation of the etiology of hepatocellular carcinoma, the quantification of the association between psychological stress and coronary heart disease and the identification of several dietary and other important risk factors in the etiology of a number of cancers and other diseases.

Welcome and Tribute

Michelle Williams, Chair, Department of Epidemiology, Harvard T.H. Chan School of Public Health

Murray Mittleman, Harvard T.H. Chan School of Public Health

Just beyond one year to the day after his passing (December 1, 2014), **Michelle Williams** welcomed speakers and guests to the Harvard T.H. Chan School of Public Health full-day memorial symposium honoring and celebrating the life and legacy of dear friend, colleague, and mentor Dimitrios Trichopoulos. Following a brief summary of Dimitrios' tremendous career accomplishments, Michelle expressed deep gratitude to all those who chose to participate in the special day of remembrance. "Dimitrios will long be remembered for his generosity and genuine kindness as a teacher and mentor," said Michelle, noting personal characteristics that would be repeated again and again throughout the day. "His inspiring legacy as a scholar, mentor, and friend is well represented by the legions of junior faculty members and colleagues around the world who were fortunate to have spent some time in his orbit." Dimitrios was committed to ensuring that generations of students would be prepared to improve the lives of others through research, teaching, and practice based on a shared long-lasting love affair with the discipline of epidemiology, of which he said: "Epidemiology is not just an expansion of statistics or good training in medicine or biology, it's a discipline with distinct intellectual elements and a broad core of essential principles."

Next at the podium to deliver a tribute to Dimitrios was Harvard Chan Professor **Murray Mittleman**, who shared former Harvard Chan Chair of Epidemiology **Hans-Olov Adami's** reflections on his longtime friend and colleague:

> "I always thought of Dimitrios as a Greek island… a unique, sharply delineated landscape elevating over the Aegean surface, impressively monumental from a distance, but friendly, welcoming, warm, and generous as you entered his territory. Mutual respect, limitless loyalty, deep appreciation, and occasional respectful disagreement were the fundaments of our friendship. Dimitrios combined such insight with his intellectual brilliance in a lifelong pursuit of discovery to expand the realm of human knowledge. As scholars, we meet many remarkable individuals, yet few rise over the horizon like Greek islands and remain unforgettable. Fewer, if any, change our lives. Dimitrios changed my life in ways that make me feel profound gratitude."

PART 1: A TOUR THROUGH THE SCIENTIFIC CAREER OF PROFESSOR DIMITRIOS TRICHOPOULOS

Early-Life Origins of Breast Cancer

Pagona Lagiou, University of Athens Medical School

Stem Cells and Perinatal Factors for Breast Cancer Susceptibility: Finding from Umbilical Cord Blood Studies

Chung-Cheng Hsieh, University of Massachusetts Medical School

Pagona Lagiou, longtime colleague of Dimitrios, delivered the symposium's first presentation, focusing on an important discovery he and colleagues made decades ago. Even though most female breast cancer occurs after menopause, Dimitrios and others were the first to propose that origins of the disease are established much earlier in life. In 1990, his paper in the *Lancet* hypothesized that risks of developing breast cancer in adult life may be determined by exposures in utero. The scientists presented evidence suggesting that concentrations of particular hormones, including estrogens that are at least tenfold during pregnancy, increase the risk of breast cancer in daughters while in the womb.

Several factors comprising the hypothesis are worthy of consideration. First is the extremely long period of latency (decades) between exposure and outcome, making it difficult to study subjects over time. Pagona noted that the breast is the only organ not fully differentiated at birth. Mammary tissue undergoes most of its development during pregnancy and lactation, regressing after menopause. Highlighting findings from multiple studies, she discussed several in utero and perinatal

risk factors related to Dimitrios' hypothesis, including the synthetic estrogen DES, birth weight, breast density, and mammary tissue-specific stem cells. Additional factors, including height, BMI, number of pregnancies, and lactation, play a role during later stages of life.

Chung-Cheng Hsieh presented additional findings from umbilical cord studies supporting the hypothesis that perinatal factors increase breast cancer susceptibility. The risk of developing breast cancer correlates directly with the number and vulnerability of stem cells in mammary tissue, which can be detected in umbilical cord blood samples, explained Chung. His research shows that daughters born from preeclamptic pregnancies are less than half as likely as normal birth females to develop breast cancer in adult life. The reasons for this involve the differential expression of many proteins and lower levels of stem cells associated with preeclamptic pregnancies. Chung says future studies are required to explore whether prenatal modulation of protein exposures might impact the evolution of breast stem cells into breast cancer later in life.

In summary, breast cancer etiology is a life-long journey. According to the National Cancer Institute, it is becoming increasingly evident that early-life events and exposures have important consequences for cancer development later in life. This is facilitating a paradigm shift in cancer research that could lead to more effective early-life interventions.

EPIC (European Prospective Investigation into Cancer and Nutrition) Cohort Studies

Elio Riboli, Imperial College School of Public Health (London)

Isabelle Romieu, International Agency for Research on Cancer (Lyon, France)

Elio Riboli began his talk by recalling the humbling experience of sitting next to Dimitrios in Olli Miettinen's epidemiology class at HSPH in the early eighties. Elio felt privileged to witness the critical thinking skills of such a brilliant epidemiologist, whose passion for lifelong learning was contagious. The paths of Elio and Dimitrios crossed again in the late eighties when they were both researching the relationship between second-hand smoke and lung cancer. Dimitrios, who was always eager to understand underlying reasons, consistently encouraged Elio and others to move beyond epidemiological statistics, think in biological terms, and ask insightful questions that facilitate meaningful research outcomes. Adopting that perspective, he and Elio were able to show that many of the lesions found in smokers' lungs were also present in nonsmokers exposed to second-hand smoke.

In the nineties in Europe, an active debate arose about how to best explore the links between cancer and nutrition. It had long been thought that water sources were underlying causes of cancer, but many scientists were calling for prospective cohort studies to deeply examine and enhance the understanding of the impacts of dietary and lifestyle patterns. Dimitrios played a key role in this effort, pressing those organizing what would become the expansive and complex European Prospective Investigation into Cancer and Nutrition (EPIC) study to carefully consider, explain, and prove that the data they planned to collect and analyze would lead to tangible benefits not already achieved by previous research initiatives.

In the early 2000s, as part of the European Commission-funded EPIC-Elderly study, Antonia and Dimitrios Trichopoulos spearheaded more than a decade of visionary research on healthy ageing, focused on the Mediterranean Diet. When the "Mediterranean Diet Score" was published in the *New England Journal of Medicine* in 2003, Dimitrios had once again demonstrated not only his exceptional ability to lead colleagues through debate but also his remarkable intellectual capacity to solve complex problems.

Isabelle Romieu, who also met Dimitrios at HSPH, shared her perspectives on his additional contributions to the EPIC study. Dimitrios' visionary findings in the early nineties about the impact of exposure to hormones during pregnancy have led to significant discoveries about breast cancer. Among them is the dual impact of pregnancy—stimulating replication of stem cells and thus introducing a short-term risk, but also providing long-term protection via permanent structural changes to breast tissue. However, first-time pregnancy at a later age diminishes the protection effect. Isabelle also presented research about the critical window of exposure to hormones during adolescence, noting that early puberty increases the risk of breast cancer. Many EPIC papers have also identified exposure to various hormones later in life as being important to understanding the etiology of breast cancer.

As part of the EPIC study, European countries also have been working together to better understand the causes of liver cancer. In the eighties, in one of the first major epidemiological studies on the topic, Dimitrios proved a strong association between tobacco smoking and liver cancer in the absence of confounding factors such as hepatitis and alcohol consumption. Just a few years ago, he led a landmark EPIC cohort study examining the contribution of smoking to liver cancer in ten Eu-

ropean countries, the largest investigation of its kind to date. This work has inspired numerous additional EPIC investigations of lifestyle factors and underlying metabolic mechanisms associated with the disease. One interesting recent finding suggests that drinking coffee lowers the risk of liver disease, diabetes, and esophageal cancer, thereby improving one's life expectancy.

The CHANCES Consortium

Christina Bamia, University of Athens Medical School

The Greek National Survey on Health and Nutrition (HYDRIA Project)

Androniki Naska, University of Athens Medical School

Christina Bamia summarized the accomplishments of the 2010-2015 CHANCES (Consortium on Health and Ageing: Network of Cohorts in Europe and the United States), spearheaded by Greece's nonprofit Hellenic Health Foundation (HHF), which will soon be named after its former president, Dimitrios. Underlying drivers of this global collaborative consortium included the mounting challenge of addressing diseases associated with ageing given the continuing upward trajectory in life expectancy. Since the ultimate goal is not only living longer but living well, the fifteen institutions comprising CHANCES set out to discover ways for older adults to avoid disease, maintain high cognitive and physical function, and more fully engage with life. CHANCES aimed to analyze and harmonize data collected from more than one million participants in previous prospective cohort studies as part of an effort to more accurately identify and assess risk factors, including biological mechanisms and lifestyle habits, and make informed recommendations for healthy ageing.

In concluding the CHANCES project, participants gathered in Athens in early 2015 for a dissemination workshop during which they summarized what had been learned about healthy ageing in the twenty-first century. Among the many conclusions drawn by CHANCES regarding lifestyle choices was the fact that it is never too late to quit smoking; benefits are evident even very late in life. In addition, healthy eating after age sixty can add two or more years to life expectancy. At the closing workshop, Antonia Trichopoulos noted that "CHANCES produced novel and strong scientific evidence on the determinants of healthy ageing in Europe, including modifiable behaviors, nutritional factors, and environmental exposures. These results can be used to shape the agenda of European public health policy for the elderly… and offer them a good quality of life."

Androniki Naska shared highlights from another major study initiated in Greece, outlining the health and nutritional characteristics of the Greek population that provided the rationale for the HYDRIA Project, a national health survey designed to evaluate health status and lifestyle choices. Driven in part by increasing prosperity and advances in food science, the eighties and nineties brought profound changes in eating behavior in Greece. By the late nineties, more than half of Greece's young adults (over age 25) were smoking, more than half of all men were overweight, few were exercising regularly, many were abandoning the Mediterranean Diet, and hypertension and diabetes were on the rise. But it was not until 2012, ironically during the country's worst modern-age financial crisis, that the Hellenic Health Foundation received funding for the HYDRIA Project.
Since this ongoing study began in 2013, more than 4,000 Greek adults have been surveyed. At the start, Dimitrios played a key role in informing the public about the project's objectives and encouraging participation. In fact, the vast majority of HYDRIA participants have said that the broadcast message from the well-respected Professor Trichopoulos influenced their decision to participate. The HYDRIA Project delivered hard data for earlier speculations about public health issues in Greece, including obesity. Results show that approximately 70 percent of the Greek population are either overweight or obese. More than 11 percent are prediabetic, and 42 percent recorded high blood pressure, with a significant portion of known cases left untreated. Cereals, dairy products, and vegetables are popular food groups for Greeks, but the study also pointed to a considerable increase in meat consumption among the young as opposed to greater adherence to the Mediterranean Diet among those over age 65. Combined with a decrease in physical activity, these eating habits are believed to be contributing to high rates of obesity.

Reflections

David Hunter, Acting Dean of the Faculty, Departments of Epidemiology and Nutrition, Harvard T.H. Chan School of Public Health

As both a student and colleague of Dimitrios, **David Hunter** remembered how he never used any slides or overheads when teaching. Without props, his engaging and articulate delivery kept listeners in the lecture hall spellbound. Continuing to recall Dimitrios' gifts as a skilled communicator, David remarked, "I don't think I ever sat down with him and didn't feel

better when I stood up." He was a consistently optimistic builder of science and careers. Even when he delivered criticism, he did it in the most courteous and respectful way. Drawing hearty laughter from the symposium audience, David recalled writing a commentary several years ago, about which the always astute Dimitrios said "I loved your scholarly article; too bad you published it in the wrong journal." Dimitrios would often begin correspondence to a student or colleague by saying something like: "Please forgive my lack of knowledge, but…" and would then precisely pinpoint the scientist's specific methodological flaw or statistical mistake.

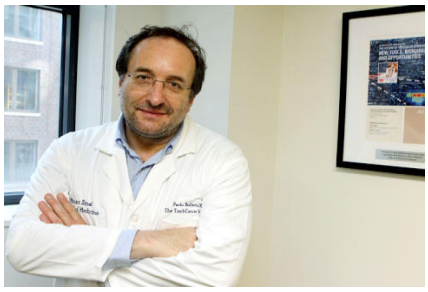
"He was our Jason, sailing between the different islands of scientific inquiry, and it was a great honor for me to be an Argonaut in his crew while he searched for truth in cancer epidemiology."

Frequently and distinctively kind and generous, Dimitrios often acted with others' best interests in mind. Citing one example, in the nineties, he suggested to the Harvard Chan dean at the time that his appointment as the Vincent L Gregory Professor of Cancer Prevention be shared with David to enhance his career. As the current Acting Dean of Faculty, David assured symposium participants this is not the norm in academia.

Dimitrios was also known for his stamina, dedication, and undiminished drive to help solve public health issues. Soon after being named chair of the Harvard Chan Department of Epidemiology, he suffered a heart attack, forcing a short stay at Deaconess Hospital. Just a few days later, chafing to get back to work, Dimitrios checked out of the hospital, walked down Longwood Avenue, suitcase in hand, and returned directly to his office. While researching his bibliography, David found that Dimitrios' final year, 2014, at age 75, was his most prolific in terms of publishing papers.

Major Preventable Risk Factor of Cancer: Tobacco Smoking and Hepatitis Viruses

Paolo Boffetta, Icahn School of Medicine at Mount Sinai



Paolo Boffetta began by referring to Dimitrios' 1980 study showing associations between smoking, hepatitis B, and liver cancer. Ten years later, Dimitrios organized the first case control study to show the correlation between hepatitis C and liver cancer. Findings from both of these early studies on the topic were replicated many times and had significant impact. We now know that hepatitis B and C viruses are responsible for nearly 90 percent of liver cancer cases worldwide. Also in the early eighties, Dimitrios and Brian MacMahon published the first analytical studies to provide strong evidence linking second-hand smoke and lung cancer, leading to today's knowledge of passive smoking as an established cause of the disease in nonsmokers. In 2012, Paolo published a study finding that 24 percent of lung cancers in female Chinese nonsmokers were attributable to second-hand smoke.

Paolo and Dimitrios worked together on the EPIC Greece prospective study, finding the presence of a protein called CRP in multiple kinds of cancer. This was the first comprehensive analysis of chronic inflammation markers across the broad spectrum of cancer cases in Greece. As part of the European EPIC cohort led by Dimitrios several years ago, the two collaborated again to study major modifiable risk factors (hepatitis, BMI, alcohol, and smoking) for liver cancer. Their findings, published in 2011, represent a continuum of the work begun by Dimitrios decades earlier.

Paulo says he learned many important lessons from Dimitrios. First, take advantage of population characteristics to study public health issues, as Dimitrios did in Greece. Second, always link epidemiological observations with medical/biological rationale. Third, carefully consider sources of bias. Most importantly, cautiously interpret findings by replicating them in subsequent studies.

Mediterranean Dietary Pattern for Health

Frank Sacks, Harvard Chan School

Frank Sacks began his talk by explaining how he, Dimitrios, and others were perplexed by the nutrition science orthodoxy of the nineties, which advocated a low-fat diet as the best way to get rid of saturated fat. Essentially, fellow scientists were promoting a low-fat junk food diet. In collaboration with others, Frank and Dimitrios set out to change the paradigm regarding what comprised a healthy diet. For starters, they agreed that one cannot possibly be expected to enjoy eating veg-

etables without olive oil! Next, yielding to the power of pyramids ruling health guidelines at the time, Dimitrios and others proposed the "Healthy Mediterranean Diet Pyramid" as an alternative to the low-fat approach. A 2003 study by Dimitrios and Antonia, published in the *New England Journal of Medicine*, showed that Greeks who adhered to the Mediterranean Diet significantly reduced their risk of dying from coronary heart disease or cancer. This was one of many studies that would debunk the low-fat frenzy.

Numerous clinical trials have provided evidence that the Mediterranean Diet lowers blood pressure and cholesterol, helping to persuade those in doubt that a diet high in unsaturated fat can reduce risk factors for heart disease. Harder to prove was the fact that a high-fat diet can lead to long-term weight loss. But, in 2001, Frank and colleague Kathy McManus (Brigham & Women's Hospital) showed that overweight study participants who followed the Mediterranean Diet or a low-fat diet lost weight. However, after eighteen months, only those on the low-fat diet started to regain weight. Dietary variety and enjoyment of food are associated with greater adherence to a diet and sustained weight loss. If that's not enough reason to become a believer, one study shows a 25 percent improvement in erectile function after two years on the Mediterranean Diet. "If you change your diet, and you're having good sex, you might sleep better too," suggested Frank. A 2011 study showed that Mediterranean Diet followers experienced fewer sleep apnea episodes. Perhaps that, in turn, leads to better thinking. A 2013 study suggests that consuming olive oil lowers the risk of cognitive impairment and boosts scores on mental state exams.

The Canon of Medicine

Albert Hofman, Harvard T.H. Chan School of Public Health

In 1997, the *Lancet* published Richard Horton's "A manifesto for reading medicine," a canon of twenty-seven papers he identified as must-reads from two-and-a-half millennia of publications. Included are several papers from the field of epidemiology on lung cancer, TB, and coronary heart disease. Among this select group of highly regarded research papers is Dimitrios' 1983 study showing a significant increase in fatal heart attacks immediately following the 1981 Athens earthquake. **Bert Hofman** said this paper, which he described as straightforward, concise, and beautiful, clearly deserves to be part of this exclusive collection.

While recounting Dimitrios' most memorable characteristics, Bert remembered how some students returned year after year to attend essentially the same lecture delivered by Dimitrios at an annual conference at the Erasmus Medical Center in Rotterdam. His teaching talents were just so wonderful and inspiring to experience. Dimitrios also demonstrated astute, clinically oriented judgment, especially when it came to evaluating diseases, said Bert, who suggested he may have come by this trait partly due to the fact that his father was a surgeon. Bert referred to views expressed in 1928 by the father of epidemiology in Europe, Major Greenwood, who said that scientific epidemiology—like most things that make life worth living—begins with "little sums." Bert speculated that Dimitrios likely possessed a similar sensibility. He too preferred basic epidemiological methodologies as opposed to complex statistical models.

> **"Dimitrios was a splendid man, a great and creative scientist, and a true Hippocratic epidemiologist. I miss him."**

Ollie Miettinen, the renowned Harvard Chan professor of epidemiology, emphatically told his students that there was no such thing as "natural experiments," which he called a contradiction in terms and utter nonsense. When Bert reminded Dimitrios of this following the publication of Dimitrios's Athens earthquake natural experiment paper and Miettinen's metro experiment paper in the mid-eighties, Dimitrios noted that as a lifelong epidemiologist, "it is important to be principled but not dogmatic."

Cold, Heat, and Coronary Mortality

Kenneth Rothman, RTI International and Boston University

Last year's Cutter Lecture speaker **Ken Rothman** knew Dimitrios for forty-five years, mostly as a friend, but they did collaborate on several projects. Regarding perhaps one of Dimitrios' lesser-known interests, he reached out to Ken about research he wanted to do on coronary mortality and the environment. While coronary heart disease is declining, it remains the major cause of mortality in the US. It was known that the frequency of coronary mortality was higher in winter months, but Dimitrios wanted to explore whether this seasonal pattern had changed over time.

Ken and Dimitrios discovered a way to measure the intensity of the cyclic seasonality pattern. They plotted and analyzed nearly sixty years of data Dimitrios had collected, including the number of coronary deaths in every month of the year, from the mid-1930s to the mid-1990s. The seasonal intensity was still there, as evidenced by a midwinter peak in heart disease deaths every year, but the two scientists correctly theorized that this seasonality effect would show a decrease over time. As people began to move from rural areas into cities, more worked in heated environments and fewer were exposed to winter's frigid temperatures. Mission accomplished… well, not quite yet. Dimitrios was intrigued by what appeared to be a very slight resurgence of the winter seasonality factor after 1970. He convinced Ken that additional investigation was necessary. It turns out that the declining trend in the winter pattern had been somewhat offset by summer heat waves that caused fatal heart attacks. However, with the advent of air conditioning, there was less of a summer peak to counter the winter peak, hence the slight uptick in winter seasonality impact after 1970.

Earlier Life Exposures and Risk of Breast Cancer

Walter Willett, Harvard T.H. Chan School of Public Health

Much of Dimitrios' interest in breast cancer focused on the impacts of early-life experience, noted **Walter Willett**, who began his talk by highlighting a 1969 study on lactation and reproduction histories of Greek breast cancer patients. This paper was coauthored by Antonia Polychronopoulou, who would later share not only a long family life with Dimitrios but also an enduring professional partnership that yielded many important findings, particularly in the field of nutritional epidemiology. The 1969 study was also coauthored by Brian MacMahon, who Walter noted was especially skilled at identifying and connecting smart, creative people for productive collaboration. Beyond Dimitrios and Antonia, this early study helped to forge significant bonds that linked Dimitrios and Greece to Harvard and Boston, planting the seeds of what would become an impressive lineage of accomplished epidemiologists.

Early collaboration between these scientists was the precursor to a comprehensive series of investigations known as the Nurses' Health Study (NHS), involving more than 18,000 women and running from 1976 until 2000. Early on, the researchers involved realized that by studying only women who were over 30 years old, they were missing what epidemiological data indicated was a critical period of exposure for breast cancer risk. In the nineties, NHSII included younger adults as part of an effort to address this gap. Surveying study participants about their dietary habits as teenagers revealed a significant relationship between red meat consumption and breast cancer risk in premenopausal women. They found that when red meat was replaced by other sources of protein, the risk of breast cancer in this age group was reduced by 23 percent. Related studies found an inverse relationship between adolescent fiber intake and breast cancer risk and, as in many other studies, a significant association between even moderate alcohol consumption and benign breast disease.

The unanticipated finding of a strong inverse relationship between childhood obesity and risk of breast cancer in pre- and postmenopausal women remains an enigma. Studying breast cancer can be both humbling and humiliating, said Walter. You believe you know something to be true, and then research proves exactly the opposite, as was the case with the BMI findings. In closing, Walter noted that one of Dimitrios' greatest contributions was leaving behind a couple of generations of tremendous epidemiologists and wonderful colleagues who will keep us all connected for many years to come.

Aspects of the Mediterranean Diet and Disease Risk

Carlo La Vecchia, University of Milan

Carlo La Vecchia never met Dimitrios, but they talked on the phone a lot; pancreatic cancer, liver cancer, and diabetes were among the diseases they discussed. Dimitrios gave Carlo a book by Sherlock Holmes creator Arthur Conan Doyle, highlighting the observation that while it is easy to follow a story, "in solving a problem… the grand thing is to be able to reason backward." Such are among the challenges scientists face when conducting case control studies.

Dimitrios and Carlo studied the impacts of the Mediterranean Diet. In particular, they looked at flavonoids, compounds and antioxidants found in fruit and vegetables that may be responsible for helping to lower the risk of stomach, kidney, colorectal, oral, throat, and especially upper digestive tract cancers. They also discovered that an increased intake of flavonoids reduces the risk of both breast and ovarian cancer.

Digging deeper, they and others conducted a half dozen epidemiological studies on the relationship between olive oil consumption and breast cancer risk, which all showed a strong inverse association between the two. It is not entirely clear

whether reduced cancer risk is due to the fatty acid in olive oil or the presence of antioxidants and other components in olive oil… as well as in other foods associated with the Mediterranean Diet. Among several interesting findings, they were able to show that those adhering to the diet may not only be able to maintain body weight but also potentially lose weight, a priority for cancer prevention. In closing, Carlo noted that a higher Mediterranean Diet score proves to not only reduce the risk for the cancers mentioned above (plus endometrial and pancreatic) but also lowers the chances of contracting hepatitis, diabetes, and heart disease.

PART II: TAKING PROFESSOR DIMITRIOS TRICHOPOULOS' LEGACY TO THE FUTURE

Pagona Lagiou moderated the symposium's afternoon session, dedicated to remembering Dimitrios' unparalleled dedication to helping his students succeed. His passionate curiosity and pursuit of unusual ideas invigorated those who worked by his side. He often told young investigators that hard work, perseverance, and the ability to stand back up after falling down account for the difference between success and failure in science. His favorite example of heeding this advice was when the *New England Journal of Medicine* chose not to publish his paper on passive smoking and lung cancer, explaining that while "the implications of your findings are enormous, and we believe that you will be proved right, the editors could not find your arguments persuasive enough…" Dimitri clearly stood right back up after this "fall." The paper appeared in the *National Journal of Cancer* in 1981 and became the most quoted source of his work.

> **"Believe in the work you are doing, be ready for successes, and more so for failures, which are bound to exist. It's a rule of life. The only way to avoid failure is to not do anything, and this is not an acceptable alternative."**
>
> -Dimitrios Trichopoulos

Dimitrios had a very effective system for selecting doctoral students. The current mentee would choose the successor, making sure, per Dimitrios' request, that the candidate understood his strengths and limitations as a mentor. The symposium's afternoon attendees were treated to a poignant retrospective, delivered by a panel of five doctoral students who shared their stories one after the other, in the same order that they worked with Dimitrios.

Obesity, Biomarkers, and Breast Cancer Risk in Black and White Women

Loren Lipworth, Vanderbilt Ingram Cancer Center

Loren Lipworth worked with Dimitrios from 1999 to 2013, mostly at HSPH. They studied hormone levels in maternal and umbilical cord blood in Caucasian and Chinese women and their newborns. They found significantly higher levels of the hormone IGF-1 in white women, which correlated with higher birth weight. Their findings suggest that this hormone may be an important factor in fetal growth, which other studies have confirmed is associated with stem cell proliferation and increased breast cancer risk. In a related study, Loren and Dimitrios showed that early exposure to IGF-1 influences adult height, another risk factor for breast cancer.

> **"Dimitrios was the most inspiring teacher I ever had. He is the reason I became an epidemiologist. He instilled in me a work ethic and humility that have permeated my life. He was so incredibly generous with his time and knowledge."**

Loren is currently working on two projects that bring her full circle back to Dimitrios. As part of the expansive Southern Community Cohort Study, looking at obesity and breast cancer risk among more than 86,000 generally low-income women in the southeastern US, she and colleagues seek to determine which obesity-related biomarkers are associated with different types of postmenopausal breast cancer in black versus white women. The other project involves linking phenotypes to Electronic Medical Records over the course of a lifetime to examine such associations as those between maternal and infant characteristics and obesity later in life.

A Time Honored Ethos: Mentoring in the Method of Dimitrios Trichopoulos

Lisa Signorello, National Cancer Institute/National Institutes of Health

We know that mentoring provides a foundation for academic success, but we don't necessarily know precisely how to do it well. It can be learned but not necessarily taught, says **Lisa Signorello**, the second of Dimitrios' mentees to share her sto

ry. She believes that she and her fellow panelists are meant to continue the tradition of helping to develop young investigators, paying forward all that Dimitrios taught them. In her current position as the deputy director of the NCI's Cancer Prevention Fellowship Program, she thinks a lot about what it means to be a good mentor. She knows it involves things she learned from Dimitrios: setting the bar high as a role model, making a strong commitment, and sharing insights and techniques. In her career, Lisa says mentoring gives her a lot of energy. She sees it as a privilege and an opportunity to expand in new directions.

> **"I believe there is nothing I cannot accomplish, and that feeling comes directly from Dimitrios. He has been called a giant in cancer epidemiology, but he was also a giant in so many other respects. For us, he was the pivotal person in our professional and personal growth."**

As a mentor, Dimitrios allowed his mentees to contribute to collaborative work not as students but as equals. He included them in endeavors well beyond their thesis work, broadening their expertise and giving them the opportunity to work with accomplished investigators worldwide. He instilled in them the skills and confidence to pursue successful careers. When they left Harvard and Dimitrios, explained Lisa, they felt prepared to contribute, respond to challenges, and join forces with the global scientific community.

Disability in Low-Income Countries

Hannah Kuper, London School of Hygiene & Tropical Medicine

Unlike the others on the afternoon panel, Dimitrios' next doctoral student, **Hannah Kuper**, chose to pursue a career focused on disability in impoverished countries rather than cancer epidemiology. Dimitrios was somewhat baffled by this choice, according to Hannah, who said he did not quite understand why she would want to venture far and wide to dangerous places when there was perfectly good research to be done in the UK, Europe, and the US. Conducting epidemiological research about disability in low-income countries is indeed difficult, but Hannah relishes the challenge.

> **"Noel Coward said: 'Work is much more fun than fun.' Dimitrios loved to work not only because he was incredibly intellectually stimulated by what he was doing but also because he made work fun by surrounding himself with colleagues who he turned into friends."**

Limited by resource constraints, Hannah and her colleagues rely on relatively fast and flexible case control methodologies developed by Dimitrios to study disabled populations in poor environments. The information they gather is critical for assessing impact, enabling advocacy, and planning services. Her cataract blindness case control study in Kenya, the Philippines, and Bangladesh revealed that the visually impaired are even poorer than their neighbors. Many of the subjects were offered surgery that reversed their blindness and improved their financial circumstances. Another study in an extremely disadvantaged part of Kenya experiencing severe food shortage provided evidence that children with disabilities are twice as likely to be malnourished. Case control studies in Peru and Tanzania unfortunately show that those with disabilities, who are in the greatest need of social protection programs, are not more likely than others to be beneficiaries of such support.

Prostate Cancer Epidemiology

Lorelei Mucci, Harvard T.H. Chan School of Public Health

As was the process described earlier, Hannah introduced **Lorelei Mucci** to Dimitrios. Lorelei remembers being terrified that afternoon, but within fifteen minutes, Dimitrios' warm kindness and generosity—qualities he highly valued in other scientists—made her feel like part of the family. Even though they did not work together on prostate cancer, Lorelei chose this special day to share a recent study on the topic. This research exemplifies many of the principles she learned from Dimitrios, who she believes would be proud to know it was the only epidemiological paper selected by the *Journal of Clinical Oncology* for inclusion in its top ten publications of 2015.

The study of 49,000 men age 40 to 75 was a follow-up to the Health Professionals Study in the nineties that explored the relationship between vasectomy and prostate cancer, an important public health issue that Lorelei and colleagues believed was worthy of additional investigation. After all, 15 percent of adult men in the US (about 500,000) undergo the procedure every year, and there was some conflicting data and debate in the literature. Some earlier studies hypothesized that increased prostate cancer risk might be attributable to the intensity of PSA screenings rather than vasectomy.

"Today, each of us showed pictures of Dimitrios with our kids without knowing the others planned to do this. Dimitrios loved our children. He was the first person to meet my son, Ethan, in the hospital right after he was born. I'm so grateful for the impact he had on my professional, personal, and family life, and I really miss him."

Dimitrios always encouraged his students to be bold but also to continuously doubt and challenge their hypotheses… and painstakingly seek the truth. Following in his footsteps, Lorelei and her team exhaustively analyzed the study data and tested their contrarian hypothesis, ruling out every potential bias and confounding factor that could account for elevated risks associated with vasectomy. They documented a statistically significant, albeit small, increase in the risk of advanced or lethal prostate cancer among those who had had a vasectomy.

Mammographic Density and Breast Cancer Risk

Rulla Tamimi, Harvard Medical School, Harvard Chan School

To the delight of Dimitrios, **Rulla Tamimi**, like her predecessor Lorelei, remained in Boston following her doctoral studies. Rulla says she sort of "snuck into" Dimitrios' close-knit family of mentees. Rather than being nominated by Lorelei, she was actually introduced by the previous mentee, her friend Hannah Kuper. Still engaged in course work and unsure if she was prepared to embark on an apprenticeship with Dimitrios, he quickly downplayed her uncertainties, and the two established an immediate connection. They exchanged ideas about Mediterranean culture and religion, formed, in part, by the fact that both their mothers hailed from Egypt.

Like earlier speakers, Rulla referred to Dimitrios' 2008 paper on early-life events, remarking on how well the research reflects his voice and holistic approach to understanding the etiology of breast cancer. She explained how he was always trying to fit together all the pieces that comprised what they knew about the disease. Dimitrios was so well versed in all the different elements, and Rulla admired the way he masterfully synthesized input to create a model, and then test and refine a hypothesis.

"As the patriarch, Dimitrios fostered an amazing family environment for us. These women are my sisters in science. We worked together, traveled together, and laughed and cried together. I feel very fortunate I was invited to be a part of this special family."

In the 2008 study, Dimitrios and others showed that mammographic density is determined very early in life. Following in his footsteps, Rulla continues to study breast tissue density, one of the strongest risk factors for breast cancer. Women with 75 percent or more dense breast tissue are four plus times likelier than those with predominantly fatty tissue to be diagnosed with breast cancer. In 2010, she worked with Dimitrios on a paper linking birth size and weight to mammographic density in postmenopausal women in Sweden.

Like Dimitrios, Rulla has studied the relationship between hormonal exposure, mammographic density, and breast cancer. Her research findings include evidence that postmenopausal women with the highest hormone levels coupled with the highest density in breast tissue carry the greatest risk of developing breast cancer. Sharing Dimitrios' view that mammographic density is established early in life, Rulla intends to identify additional risk factors that differentiate those women with high mammographic density who carry the greatest risk of developing breast cancer.

Closing Remarks

Fran Cook and Michelle Williams, Harvard T.H. Chan School of Public Health

Harvard Chan Professor **Fran Cook** spoke briefly about Dimitrios' contributions to the Harvard Chan Department of Epidemiology, founded by Brian MacMahon, who served as chair for thirty-one years. When Brian stepped down in the eighties, it was logical for Dimitrios, his close friend and colleague, to take the helm. Dimitrios not only sustained Brian's vision, he also laid the foundation for the department's subsequent growth. As a talented leader, Dimitrios extracted the best from people, not by forcing them to do something but by slowing engaging them. He would often say that he didn't have the adequate knowledge or experience to take on a particular task, but "you… you would be perfect for this."

Dimitrios was a strong believer as well as active practitioner when it came to teaching epidemiology. A book he coauthored on the subject is now in its fourth edition. He was also a strong supporter of teaching clinical epidemiology, planting the seeds for what is

now called outcomes research. In fact, he led the effort to introduce Harvard's first nontraditional degree program, a summertime masters of epidemiology designed for clinical practitioners.

> **"Dimitrios was a giant in research who treated everybody as special. We were truly favored to have him as a friend and colleague."**

In closing the symposium, **Michelle Williams** honored Dimitrios' wife and colleague Antonia Trichopoulos, thanking her and others at the University of Athens for sharing Dimitrios with the Harvard Chan School for so many years. "As we celebrate Dimitrios today, we thank you and recognize your contributions as a partner and spouse to a person we loved dearly."

"On behalf of myself and my colleagues in Greece, I want to express my thanks for accepting Dimitrios into your Boston family of Harvard. Dimitrios was very happy here. Most of the time I was in Greece, but knowing how happy he was here with you allowed me to share him with you. Thank you for having him. I hope these relationships will continue into the future.

-Antonia Trichopoulos

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