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A Conversation with Joseph F. Fraumeni, Jr.

Robert N. Hoover

Joseph F. Fraumeni, Jr., was born on 1 April 1933 in Boston, MA. He received his AB degree from Harvard College and MD from Duke University, followed by a medical residency at Johns Hopkins Hospital and the Memorial Sloan-Kettering Cancer Center. In 1962, he joined the Epidemiology Branch of the National Cancer Institute (NCI) as a commissioned officer in the US Public Health Service (PHS). Except for an academic year at the Harvard School of Public Health, where he received an MSc degree in 1965, Dr. Fraumeni has spent his entire scientific career at NCI. In 2012, he stepped down as director of the Division of Cancer Epidemiology and Genetics, and currently serves as a senior advisor and investigator at NCI. Dr. Fraumeni is the recipient of numerous honors, including the John Snow Award (American Public Health Association), Abraham Lilienfeld Award (American College of Epidemiology), Charles S. Mott Prize (General Motors Cancer Research Foundation), James D. Bruce Award (American College of Physicians), Medal of Honor (American Cancer Society), and Lifetime Achievement Award (American Association for Cancer Research). He is an elected member of the National Academy of Sciences, Institute of Medicine, Association of American Physicians, and American Academy of Arts and Sciences.

INTERVIEW

RH: Few people start with the intent of becoming an epidemiologist. Can you describe how your own path brought you to epidemiology?

JFF: I was encouraged to consider epidemiology by Dr. Rulon Rawson, a distinguished thyroidologist who chaired the Department of Medicine at Memorial Hospital while I was chief resident. My career plans were poorly defined, but I was intrigued by patients with rare and puzzling diseases, including those associated with cancer. On teaching rounds, I was responsible for guiding Dr. Rawson to the most interesting cases on the wards. My choices led him to remark, "You are thinking like an epidemiologist. It's the patterns that you're focusing on, and that's called epidemiology." He was enthusiastic about epidemiology and helpful in identifying ways I could learn more about the field.

I received further advice from David Schottenfeld, who was serving as an oncology fellow at Memorial. I had known David since he was a house staff officer at Duke when I arrived on his medical ward as a third-year student. David told me of his rewarding experience in epidemiology as a PHS commissioned officer assigned to the CDC. When I heard that the PHS had a similar program at NIH, I applied for a position at the National Cancer Institute. It was a two-year program equivalent to a post-doctoral fellowship and it had the important advantage of satisfying my military service obligation.

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SDC Joseph Fraumeni's curriculum vitae is available with the online version of this article at http://links.lww.com/EDE/A723.
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Joseph F. Fraumeni, Jr. (right) with Thomas J. Mason (left) and Robert N. Hoover (center) discussing cancer maps in 1977. An online version of one of the several atlas of maps of cancer mortality by county by Dr. Fraumeni is available at http://ratecalc.cancer.gov/archivedatlas.

RH: Who were your most important mentors?

JFF: Following interviews at NCI, I was fortunate to be recruited by Bob Miller, a pediatrician with a doctoral degree in epidemiology. Bob had only recently arrived at NCI as chief of the Epidemiology Branch. It was a small unit, and I was the only trainee. I was naïve about epidemiology concepts and statistical methods, but the work proved exciting and I quickly recognized that my background in clinical medicine was useful in epidemiology. After two years I went to the Harvard School of Public Health for an academic year in the epidemiology department headed at the time by Brian MacMahon and George Hutchison. I practically memorized Brian's wonderful textbook on epidemiology.

On returning to Bethesda, I continued working with Bob Miller and others on studies that combined clinical observations and epidemiologic approaches.[1] Bob was an original thinker with a wry sense of humor and a flair for writing that I tried to emulate. He was a readily available and generous mentor who also encouraged independent work. We carried out a number of projects, including a multicenter study of childhood cancer that identified some new associations with congenital defects. For example, Wilms' tumor was related to congenital aniridia and other anomalies,[2,3] a syndrome that helped others to uncover the genetic mechanism responsible for this tumor. The branch also became involved in occupational studies, and I was able to complete a study of copper smelter workers that showed a dose-response excess of lung cancer associated with levels of arsenic exposure.[4] I was quickly initiated into a public-policy debate during hearings at the Occupational Safety and Health Administration, which used our finding in setting a standard for arsenic exposure in the workplace.

In addition to Rulon Rawson and Bob Miller, Alfred Knudson was an important mentor. I was inspired by his creative use of clinical and epidemiological data for a mathematical analysis that provided new insights into the genetic mechanisms of cancer. I was fortunate to work with Al when he came to NCI to help us build the genetics component of our new division in 1995.

RH: Who would you regard as having made the most important contributions to our field?

JFF: Of course, Richard Doll. He was a towering figure in cancer epidemiology and epidemiology in general. His landmark study of British doctors with Austin Bradford Hill in the 1950s pinned down the excess risk of lung cancer and cardiovascular disease among smokers. He then proceeded to identify the cancer risk in several occupational groups, including asbestos workers, and in a cohort of spondylitis patients treated with ionizing radiation. He made an extraordinary number and variety of contributions to epidemiology, including a masterful analysis with Richard Peto that quantified the population burden of cancer that is potentially avoidable.

I got to know Sir Richard when he invited me to co-edit a book on cancer trends.[5] He suggested a division of labor: I would coordinate the chapters from North American authors while he took responsibility for all others. I suggested that he write the letter of invitation to all the prospective authors, since I knew from experience how difficult it can be to solicit chapters from leaders in the field—and especially to receive them by the deadline. He agreed to do so. Everybody promptly accepted the invitation and all the manuscripts were submitted on time. Not even a day late; it was just incredible.

Someone else I feel deserves mention is William Haenszel, who was chief of the Biometry Branch when I arrived at NCI. His meticulous study of the changes in cancer incidence among migrant populations to the US drew attention to the major environmental component of various cancers. NCI has had several high-powered statisticians who have made significant contributions to epidemiology including the development of population-based cancer registries, the design

Joseph F. Fraumeni, Jr., 2006.

of clinical trials, the analysis of complex epidemiological data, and the development of risk-prediction models.

RH: What other findings over the last 50 years in cancer epidemiology do you think are particularly notable?

JFF: When I arrived at NCI in 1962, the Surgeon General's report on the health hazards of smoking was being prepared for release in 1964. But apart from tobacco the causes of cancer seemed elusive. It was like a black box. For better or worse, epidemiologic research is often motivated by themes and hypotheses that are prevalent at the time: tumor viruses in the 1960s, environmental hazards in the 1970s, dietary components and lifestyle in the 1980s. Attention to genetic factors was generally limited to familial cancer until the 1990s when genomics became the new frontier for epidemiology.

There have been so many important findings since smoking was linked to lung cancer in the 1950s. They include asbestos and other occupational exposures in relation to lung cancer, HPV for cervical and other cancers, hepatitis B and C for liver cancer, *Helicobacter pylori* for gastric cancer, estrogens for breast cancer, the major impact of obesity and physical inactivity, and studies of radiation-related cancer.

RH: What epidemiological findings, either yours or others, were the most surprising to you at the time and why?

JFF: One of the most startling relates to the diethylstilbestrol (DES) story: the discovery of vaginal adenocarcinomas among the daughters of women exposed to DES during pregnancy. This observation caused a paradigm shift in thinking about the potential importance of early-life exposures in cancer, and in other diseases as well. Another surprise was the excess risk of breast cancer reported with alcohol intake, since there didn't seem to be a good biological rationale. The relation of passive smoking to lung cancer was also unexpected, but it illustrated the power of epidemiology to detect low-level risks that may have major public health significance.

As you know, the geographic patterns of cancer have been a special interest at NCI. In the 1970s we became aware of the tremendous international variation in cancer incidence. In the US there was little variation in cancer mortality by state or region, so we were surprised to see the distinctive patterns that emerged for certain cancers when we developed color-coded maps of the mortality data at the county level (Figure 1).[6,7] That collection of maps enabled us to target a series of case-control studies in high-risk areas of the country. We soon found that the long-term use of smokeless tobacco accounted for the high rates of oral cancer among women in the rural south,[8] while shipyard exposures to asbestos accounted for the high rates of lung cancer along the southeastern coast.[9] Subsequently, an atlas of cancer maps from China revealed patterns that were even more dramatic, and we were invited to work with Chinese scientists in case-control and intervention studies in populations at exceptionally high risk of cancer, including lung,[10] esophageal, gastric and other cancers.

RH: Who have been the most notable characters in our field, and what made them so interesting?

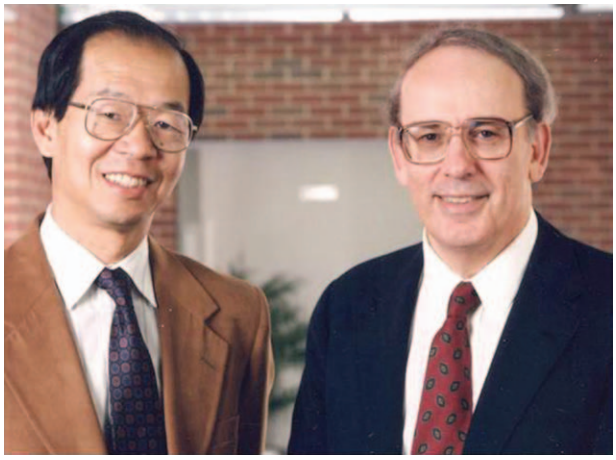
JFF: The most fascinating was Ernst Wynder. Ernst rose to prominence by being the first to establish a causal relationship between cigarette smoking and lung cancer in a study which he conducted in 1950 as a medical student. He continued to have a highly productive career in epidemiology and preventive medicine, first at Memorial and then at the American Health Foundation in New York, which he founded. Ernst always seemed to be bursting with new ideas. He was flamboyant and unpredictable, such as the time he strolled into a crowded cafeteria at Memorial in the company of a glamorous Hollywood actress. He just brought down the house.

RH: Which non-epidemiologists have been most helpful to our discipline?

JFF: At NCI and NIH we have had the consistent and strong support of our administrative leadership. In 1995, Richard Klausner, a basic scientist, became NCI director and he recognized the promise of population-based research at a national agency by elevating our program to division status. In a similar manner, John Higginson, a pathologist and director of the WHO International Agency for Research on Cancer, gave priority to epidemiology and surveillance at a multinational level.

RH: Who have been the most non-helpful?

JFF: Non-helpful? My parents told me early on never to say bad things about other people. However, you may be alluding to special-interest groups that attempt to influence the outcome of a particular study when the economic or political stakes are high. As you know, we have become tangled in several debates related to studies that could have regulatory consequences. The challenges may be unsettling at times, but they come with the territory when epidemiological research has the potential to inform public policy.



Frederick P. Li and Joseph F. Fraumeni, Jr., 1995.

RH: How has epidemiology changed since you started your career?

JFF: Of course, the methods have become more robust, but I would say the biggest change has been the specialization of epidemiology. In the early 1960s, so little was known and we were all like general practitioners. Today, many of the risk factors have been identified by traditional case-control and cohort studies. Biomarkers are often needed now to help detect susceptibility states, exposures, mechanisms, and outcomes related to cancer. In the process, there is more emphasis on prospective cohort studies that have prediagnostic and serial specimen collections, and we are interacting more with basic and clinical scientists. Another recent change has been the creation of large-scale consortia, particularly for genome-wide association studies that combine datasets for statistical power and facilitate replication of findings to avoid false-positives. This strategy has made it possible to identify the role of common genetic variants and environmental interactions for several common cancers.[11–13]

RH: What do you view as your own biggest professional successes?

JFF: I would point to progress we have made at the NCI in developing distinctive research and training programs that have helped push the boundaries of cancer epidemiology and prevention.

Of course, close to my heart is the discovery with Fred Li of an hereditary cancer syndrome that came to be known as Li-Fraumeni syndrome.[14,15] It features a wide variety of familial tumors in children and young adults, including breast cancer, sarcomas, brain tumors, leukemia, and adrenocortical tumors. Whenever possible, we collected biospecimens from family members in hopes of finding a mechanism that might explain susceptibility to such an array of different tumors. Success was limited until 1990 when a study was conducted with Stephen Friend and David Malkin at Harvard, along with Louise Strong at M.D. Anderson. The study found germline mutations of the *p53* tumor suppressor gene in several consecutive families.[16] The syndrome continues to be of special interest to basic and clinical scientists, especially since somatic mutations of *p53* are known to occur in a high proportion of cancer patients in the population.

I am also proud of the text *Cancer Epidemiology and Prevention* co-edited with David Schottenfeld.[17] David had previously published a book on cancer epidemiology while I had edited a book called *Persons at High Risk of Cancer*. David's book was oriented toward cancer sites, mine toward risk factors. We decided to join forces for a comprehensive volume that covers all aspects of cancer epidemiology. It has been a pleasure working with David on three editions, but now it's time to turn the project over to others.

RH: Over the next decade, what do you think will be the most important opportunity in cancer epidemiology?

JFF: I would say that the opportunity to incorporate some of the emerging high-throughput technologies that are rapidly coming down the pike, such as the multiplex platforms of metabolomics. I am hopeful that these kinds of studies will point to mechanisms that may be amenable to preventive intervention.

RH: What are the biggest challenges?

JFF: The challenges in genomic and molecular epidemiology—how to manage the enormous and complex datasets that are being generated, how to analyze the datasets for evidence of interactions and pathways, how to develop and integrate research and training programs in interdisciplinary research. The problems may seem daunting but I believe we will find ways to solve them.

RH: What would be the single most important piece of advice you could give to a new epidemiologist starting their career?

JFF: Find the best possible mentor that you can. Rulon Rawson at Memorial had a profound influence on my career because he was able to identify traits of which I was only dimly aware at the time. Next, find compatible collaborators who have complementary skills. When I arrived at NIH, I relied heavily on highly skilled statisticians such as Nathan Mantel, Fred Ederer, and others who were also at NCI. Then, carve out an interesting and important niche where you can eventually become an authority in that subject.

One other thing—there is almost a fear in some young investigators about large-scale collaborations or consortia. As long as you have supportive mentors and collaborators, there is no need to worry about getting lost in the crowd. It is helpful to see how team science works, and there are always projects, including spinoffs or add-ons, in which a young investigator can play a lead role. Epidemiology is so much further advanced than it was 50 years ago, but there are still major gaps in our knowledge. What are needed are new ideas, new hypotheses, new tools, and new strategies. The opportunities now are greater than ever.

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