DIVISION OF CANCER PREVENTION

ORAL HISTORY PROJECT

INTERVIEW WITH

Dr. Leslie Ford

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Biographical Statement

Dr. Leslie G. Ford currently serves as the Acting Deputy Director of the Division of Cancer Prevention, National Cancer Institute (NCI), National Institutes of Health (NIH). After earning a Bachelor of Arts in 1969 from the State University of New York at Buffalo, Dr. Ford received her Medical Doctorate from the same institution in 1974. She joined the Department of Health, Education, and Welfare in 1974 and served as Medical Officer and Chief in the Division of Peer Review and the Medical Audit Branch. In 1982 Dr. Ford joined the Division of Cancer Prevention and Control, serving as the Evaluation Specialist of the Centers & Community Oncology Program. After becoming the Chief of the Community Oncology & Rehabilitation Branch in 1987, she rose to the position of the Associate Director of the Early Detection and Community Oncology Program in 1996. In 2000 Dr. Ford became the Acting Deputy Director of the Division of Cancer Prevention. During her long tenure with the Division, Dr. Ford has received numerous awards for her work, including the NIH Merit Award and the NIH Directors Award in 2003.

Dr. Ford discusses her contributions to the Division of Cancer Prevention and her role in the development of the community oncology programs and large scale chemopreventive drug and screening trials. She emphasizes the importance of the Community Center Oncology Program and the ability to structure nationwide drug trials that have produced effective chemopreventive drugs such as Tamoxifen and Raloxifene.

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Interview with Leslie Ford
Conducted on December 17, 2008, by Philip L. Cantelon

PC: I'm speaking with Dr. Leslie, L-E-S-L-I-E, Ford.

LF: Right.

PC: On December 17th, 2008, and I have your permission to record the call?

LF: Yes.

PC: Thank you. Tell me, how does a math major come into cancer prevention?

LF: So I was a math major in undergraduate, and then went to medical school, because my mother told me I had two choices, to either do something in math or science. And never liked seeing patients, never liked practicing. Through a couple of serendipitous events, wound up doing my last three months of medical school as an intern in what was – this was back in the middle 70s, in what was originally called the Bureau of Quality Assurance. It was the last generation of the – as they say, the best and the brightest during the – it was actually even before Califano came to the department, when somebody had – it was soon after Medicare where somebody had the bright idea that Medicare should only pay for care that was of high quality and reasonable and necessary. And there was a unit set up called the Professional Standards Review Organizations. It

was legislation to set up physician organizations around the country that would be charged with reviewing the necessity and quality of care before Medicare would pay. So it's kind of a – when people talk about quality assurance now and quality care, it really had its roots in the 70s, but people don't read history. And anyway –

PC: You're breaking my heart.

LF: Yeah, right [laughter]. We had a big contract with the AMA to develop criteria for what was reasonable and necessary and high quality, and I kind of fell into that group and worked my way up to be the associate director for quality assurance. Then I went over to the HMO program, also when that became a federal mandate that HMOs be one of the plans offered, and was the director of quality assurance for the HMO program. To make a long story short, that was when Reagan was around, and there was a lot of downsizing. And they decided that the HMO program only needed administrators and not physicians or medical input, and my job was about to be eliminated and I met Jerry Yates. It was just when Peter Greenwald was starting the division. Jerry was going to be the director of community oncology and outreach, and they were looking for somebody that had some knowledge of quality assurance and how you get physicians to practice the best medicine that we know is available, and how you evaluate and measure the outcomes. And so I was hired originally as the evaluation specialist for the community programs. It was way before CCOP.

PC: Right. And what was the – were they specifically looking for someone to develop this?

LF: Well, they were specifically looking for someone to develop the evaluation.

PC: Right.

LF: It was pretty unique, if you think way back when. Now we always talk about any new program has to have metrics and all. Well, this was back in 1982 when Peter Greenwald and Jerry Yates had the foresight to know that any – this was pretty sweeping to talk about community oncology, to say that physicians practicing in their communities could actually do as well as cancer center and university physicians in terms of the quality of care. And we – whatever programs we put in place, they knew that there also had to be an evaluation component where we could demonstrate, or at least measure, that hypothesis.

PC: And what was the –

LF: So the original program was called the CHOP, the Community Hospital Oncology Program. And then subsequently, we did the CCOP, but we can get into that.

PC: Okay. Tell me, what was the – I suppose the – I don't know, it's sort of a culture attitude issue here of this division and NCI, which is not – is not known as a prevention, but as a disease treatment area, and NIH being the same.

LF: Well, I'm not sure that that's true.

PC: Okay.

LF: I mean, NIH, certainly, and the Heart Institute has put a lot of resources into cardiovascular prevention. I mean, it comes across as treating high blood pressure or treating high cholesterol, but it's really prevention of heart attacks.

PC: Uh-huh.

LF: Same with osteoporosis. We treat low bone density or study how to increase bone density. Nobody really cares what your bone density is, only that it is a risk factor for fracture. So there really is, you know, subversive prevention going on [laughter]. The problem with cancer is what do you treat, atypical hyperplasia? You know, people don't buy into that.

PC: Well, was there much interest in treatment wide at NCI?

LF: Yes, but going back to the 80s, it wasn't billed as a prevention program. I mean, originally, at least what we were doing in community oncology was more cancer control than outright primary prevention. It was making sure the physicians practice the highest-quality care, that treatment benefits get diffused. It was all based on diffusion, that treatment benefits that we learned from clinical research get diffused into communities

where patients are actually being seen. It had a big rehabilitation component also. It was the very early days of treating cancer like a chronic disease and having the means to do supportive care and symptom management. So prevention kind of was the subtext of building a network across the country. If you look at the first CCOP RFA (Request for Application), it specifically talks about funding community programs to participate in NCI-approved clinical trials for the purpose of diffusing best practices and building a network to do subsequent prevention clinical trials. And it wasn't until the late 80s, early 90s that we actually got into that.

PC: And when you – you then became chief of the Community Oncology and Rehabilitation Branch.

LF: Yes.

PC: And what changes were taking place at that point in the mid-80s? Again, it's still Reagan.

LF: Yes. We went Reagan to Bush, severe budget cuts. But let me think back then. And we had a large evaluation of the first phase of the CCOP program. It was an overwhelming success. The number of the patients going on trials was increasing, and so we didn't have too much trouble. And we had had this evaluation in place, so we didn't have too much trouble getting the program funded a second time. Budgets were tight, but the science, I mean the research community was not nearly as politicized as it has been over the last

eight to twelve years, I would say. You know there weren't things like stem cells to worry about . I don't think Reagan was quite as much of an ideologue as some of the subsequent leadership. The NIH director was not as powerful as they've become. And, I guess, Bernadine Healy came in. She was a big supporter of what we were doing. So there really wasn't too much of an impact, if I remember correctly.

PC: Explain the Community Clinical Oncology Program for me, what you are trying to accomplish.

LF: So the first program we had when I came to the division was called the Community Hospital Oncology Program, and that was based on this notion that if physicians in their communities develop best practices – developed what – we called practice guidelines. You develop guidelines for how to care for patients with certain cancers and that will upgrade the quality of care because all of the physicians in the community that have participated in developing these consensus guidelines will follow them, and everything will be great. That evaluation demonstrated that these guidelines developed by community consensus usually were the lowest common denominator. And even if physicians followed them, they really didn't represent best practices on state-of-the-art care. And so the CCOP program, Community Clinical Oncology Program, instead tied this notion of diffusing quality of care to clinical trials protocols. NCI approved clinical trials that were developed through our clinical cooperative groups.

So pretty much, the clinical trials or protocols were developed more by university physicians, cancer centers, and represented state-of-the-art care versus what we thought could be a better practice, the idea being that these kind of gold standards of practice would upgrade the quality of care. That did prove to be more successful, and we were able to demonstrate that when there were positive results from clinical trials, that the community physicians who participated in the trials were more likely to pick up these new practices faster. We never got to the point of measuring outcomes for patients, like survival, because that would have been too long term, but we did patterns of care studies and were able to demonstrate that physicians did adopt the new practices.

PC: What about the nursing community?

LF: We did have a program for nursing research. Nurses were an integral part of doing any kind of clinical trials research. They're the primary support. And we also had a nursing research rehabilitation program. That was mainly through investigator initiated research, R01s.

PC: And was that later tied in with the NINR as a collaborative thing, or not really?

LF: Not really. Only to the extent that they would sometimes have an RFA that they would want joint funding on if it had a cancer focus, or if we did an RFA that had a nursing focus, we would ask them to pick up a few grants. They, actually, didn't come into being until sometime in the 90s, I think, after we had an established nursing research program.

PC: Yeah, it became an institute in '93.

LF: Yeah.

PC: It was a center on campus in '86.

LF: Right. And one of our lead nurse researchers actually went over there to run their extramural program, so in the later 90s, so that's how we contributed [laughter].

PC: Stolen or went, huh?

LF: Stolen.

PC: [Laughter]. In these years, how were the agendas set within the division for what you wanted to do? For example, let me go back to the book on – that you did with Peter on the goals – cancer goals, 1985 to 2000.

LF: Oh, yeah, the goals for the year 2000?

PC: Yeah.

LF: That seems like ancient history. I wrote the treatment chapter. And that, again, was all based on how we were going to improve outcomes for cancer patients. It was based on the assumption that improvements in outcome were based on physicians practicing what we already knew was best care. And if everybody upgraded the quality of the care they provided, to state-of-the-art care, you could get this amount of benefit to reduce mortality by the year 2000. So that's kind of the loop back. You know, how are we going to get physicians to actually upgrade their care and practice state-of-the-art care? And that's where we had these different programs, the CHOP and the CCOP, all aimed at getting physicians to practice state-of-the-art care.

PC: And did – was this book sort of the – and what you were writing in the different chapters, not just you but the division, the contributors to it, in setting those objectives, was that going to be the framework for agenda?

LF: That was the intention.

PC: Yeah.

LF: That was certainly the intention.

PC: And what happened to the road to good intentions?

LF: I wasn't that high up in the hierarchy at the time, but my impression was budgets and unrealistic expectations usually get in the way. Although, I think there were things in that, like in the treatment chapter, we did institute programs that were aimed at addressing what was there. I can't even remember what was in the other chapters because I paid not much attention to them. There probably was one about screening, and there were a number of programs trying to get women to get mammograms, and we have the prostate, lung, colon, ovary trial that actually was conceived back in the late 80s, but not implemented until the early 90s.

PC: So the agenda for the division would change as other things occurred in terms of the trials?

LF: Well, I mean you have to take advantage of opportunities. And I think the over – the overriding agenda has always been the same, to decrease morbidity and mortality through an ordered sequence of research to applications. But you have to either go with the flow, take advantage of opportunities, pull back when budgets pull back, you know, reality kind of sets in.

PC: What – did Peter always set the standard for a public health presence, public health initiative? When I say that, it's – public health in my view goes – going beyond simply the research. And I can see this with the community programs, but you came out of public health, and I think others did as well in the leadership. Was that a –

LF: So we always kind of had this two-pronged approach where we would talk about interventions in the medical community, and then interventions that were more public health related, like the anti-smoking initiatives we did, the five-a-day, the diet initiatives, things that would aim at a broader application as opposed to medical interventions or clinical trials or things that related to activities in the medical community. I think we still view the activities that way. The thing is that a lot of the more public health activities have been taken over by the Division of Cancer Control and Population Sciences. I mean that was – when we got that split, a lot of that went there.

PC: Tell me about that split. What was behind it?

LF: What do I think was behind it? I think Dr. Klausner and Dr. Greenwald didn't see eye to eye on things, and so a committee was engineered. We had a number of review committees, but there was a prevention committee, there was a cancer control committee, and the recommendation was forthcoming that the division should be split. I mean, I never – there were a number of people that I knew that were in the room and refused to sign the reports. And it was, you know, clear that it had been engineered that they were told, that membership was selected as such, and they were told what was wanted in the reports.

PC: And this was –

LF: I mean, that was my recollection.

PC: And this was really –

LF: That they wanted to kind of make – that Peter had too much power over the entire cancer control budget, and that they wanted to dethrone him.

PC: So, like many things, it's a budget issue, money issue.

LF: No, I think it was more a personality and control issue.

PC: Ah, okay. And –

LF: Because the money, I mean the money was there. It was who controlled it, and in whose likeness.

PC: [Laughter]. And so the heart of the matter wasn't necessarily where control belonged, but where the personalities –

LF: Yeah. That's what I recall.

PC: So it wasn't a scientific decision; it was a bureaucratic one.

LF: Yeah.

PC: Okay.

LF: Or a power struggle. Peter was never a yes man.

PC: [Laughter]. You have worked with him a while.

LF: Yeah. And, you know, he likes to stir up the pot, and so there are a few ways, you know, it's hard to fire him so, you know, instead, you take away some of the responsibility.

PC: And what was the remaining office's reaction to all of this? I mean how do you put humpty dumpty back together?

LF: Well, it's interesting. We have a kind of a core group of loyalists. We say we have a passion for prevention on the prevention side, and we were able to rebuild the diet and nutrition group. We brought in John Milner. So, I mean, the division survived. And a lot of us, the people that were on this, as I said, we had this kind of medical versus public health, or two-pronged approach. The people – those of us that were on the medical side, which was the part that we kept, kind of thought the other was soft science anyway, so more power to them. Let them go and do their community interventions and their surveys, and leave us to do the real work, you know, the real science.

PC: And one of the things I've also noticed is that all the branch chiefs and the like are editors, are service editors of the professional journals.

LF: Yeah. Well, they've been more. And that's fairly recent. JNCI, of course, is the oldest of them, but the AACR journals, that's been a little bit more recent that we've been asked to serve on those.

PC: When you say been asked to serve, who asked you to serve? Is that –

LF: The editors.

PC: The outside editors.

LF: Yes.

PC: But it also enables the office to keep a wise eye out for what's going on.

LF: Yes.

PC: In other words, when you review the articles and such. And I wondered if Peter had encouraged that, or is that just something that has happened? Because it seems to me rather new in the last 10 years.

LF: Yes. So I guess it started, when Barry Kramer was here. He then became the editor in chief of the JNCI. So while – if I'm not mistaken, it was while he was still here. So that kind of set the tone. I mean, obviously, Peter allowed it and that set the tone. He put a number of people from the division on the editorial board. And, I guess, it's been subsequent to that that ACR first started their CEBP (Cancer Epidemiology Biomarkers and Prevention).

PC: [Laughter]. There are a lot of acronyms. I'm going to have to –

LF: Yes, CEBP, Cancer Epidemiology Biomarkers and Prevention. So that was really the first prevention-focused journal. And a number, I guess Dave Alberts, who was one of our original grantees, was one of the editors of that. We really were the experts in the field of cancer prevention. So he asked people to be on it. And now, more recently, AACR put out the Cancer Prevention Research journal, and that is – the editor in chief of that is Scott Lippman, who was another one of our long-time grantees. And so he also asked people from the division to serve in various capacities on the journal. This is where the expertise is, really. And maybe that's different than other fields, but the, kind of the underpinnings for cancer prevention research really do lie here in DCP.

PC: That is, in –

LF: In the Division of Cancer Prevention. I think so.

PC: By, in terms of selecting the extramural awardees?

LF: Well, no, I mean in terms of the knowledge base of cancer prevention research is very firmly in this division.

PC: And that's no accident.

LF: I don't think so. And, you know, if you look around at who runs – the director of prevention and control at the various cancer centers, they probably all have – or a good many of them have come through this division, either in our prevention fellowship program or as actual employees of the division.

PC: Who move back and forth?

LF: Yes.

PC: Or you bring IPA's in.

LF: Yes.

PC: So they have a chance to work here and then go back.

LF: Yeah.

PC: And you also served on the – or I think still do, the *Journal of Women's Health*?

LF: Yeah.

PC: And they asked you to become the editor or an editor for that?

LF: I'm on the editorial board.

PC: That's what I mean, the editorial board.

LF: Yeah. And that goes back to – it's actually kind of two-pronged. That goes back originally to – that was, you know, the whole field of women's health research is only about fifteen years old now, twenty years old. I guess I'm getting older. But that goes back first to the advocacy for breast cancer research, which spilled over into an advocacy for women's health research, the old line about when they did research on women's diseases, they used mice. And not only that, they used male mice. You know, I'm sure you've heard that a million times.

PC: Yes. [Laughter].

LF: When Bernadine Healy became NIH director, this was one of her platforms was to upgrade the quality of women's health research, and that's when the women's health

initiative was started, and I was involved in that from the breast cancer prevention side. And also in the division, we had been doing a lot of the diet modification clinical trials with Carolyn Clifford that were the underpinnings of some of their interventions, their diet interventions. So I got involved back then, originally more from the breast cancer perspective, but then after Carolyn died, I took over her role in the WHI, so I've always been kind of on the – tangentially, you know, involved in the women's health initiative, but also in the whole start of the wave of recognizing women's health research.

PC: Uh-huh. Let me go back to some of these trials, which I believe you were in charge of. The breast cancer trial of Tamoxifen.

LF: Right.

PC: Why did that come about?

LF: So – as I said, when we originally wrote the CCOP RFA, the first one talked about doing treatment clinical trials in the community and building a network for eventual prevention clinical trials, we had our network in place, and we also had data accumulating about Tamoxifen. It was a drug that was used in the adjuvant setting for breast cancer, and we knew that it was relatively non-toxic. It wasn't a chemotherapy. It was hormonal therapy. And women who had early breast cancer and took it had a 50 percent decrease in their risk of getting a new cancer in their opposite breast. And so the timing seemed right. It was pretty bold, when we looked back at it, to say, "Okay, we know this can do

this in the adjuvant setting with relatively healthy women. Maybe it's time to launch our first primary prevention trial in women that are at high risk for breast cancer." And Peter gave me the ball and let me run with it. We had the CCOP. We had a system where we could implement a trial, and so we put out a request for, through the cooperative groups through our CCOP research basis to submit concepts to do such a trial. We got two concepts, one for a full-blown trial including pre and post-menopausal women, and the other for a pilot study to see if it was feasible to do it. After peer review, we decided to barge right in and go with the full-scale trial.

As they like to talk about at NSABP, Dr. Bernard Fisher, Walt Cronin and Dr. Larry Wickerham hold up the manual for how to do prevention clinical trials, and say, "When we started, this manual had no pages in it." So we really wrote the book on how to do cancer prevention clinical trials, primary prevention clinical trials. It's been quite an interesting ride.

PC: And when you identified – then when you identified high-risk people, you were identifying family?

LF: Yes. There was – there had been work done by Mitch Gail and other people in the Cancer Institute on how – on risk factors for breast cancer, and they had developed a logistic regression model from old screening data that's now called the Gail Model because Mitch was the primary author on the paper. And it was actually the NSABP, the people that we selected to do the trial that came up with the algorithm for how we would

identify high-risk women. We said that any – this was when people were talking about a breast cancer epidemic, and the rates of breast cancer were just unacceptably high, and so they chose – they said that the risk of a 60-year old woman, the lay press and advocates, that was just way too high, so we said, "Okay, if anyone has the risk of a 60-year old woman, we'll consider that high risk." And we had a way of measuring that based on known risk factors, including family history and whether a woman had any children or any biopsies. And that now has kind of become the standard by which we talk about high risk for entering trials and for people considering intervention.

PC: And what has the impact of genomic studies done on that?

LF: So when we started the trials, the "breast cancer gene" had not been identified. The development phase was '90 to '92, we started accruing in '92. There was the race to identify the breast cancer gene. That was, and I guess – I have to go back to the publication, but I think it was like '93 that it was sequenced. Might've been early '94, but I think it was '93, late '93. That was going to be the Holy Grail. Once we identified the breast cancer gene, we wouldn't need any of this because we would be able to tell who was at risk and who isn't, and then just concentrate on that group. So we identified the breast cancer gene, and it took about ten years to figure out what the function of the gene was, and since all the studies were done in this incredibly highly-penetrant families, the estimates for how much this breast cancer gene or mutation in the gene accounted for in the 100 or 200,000-odd cases of breast cancer that were diagnosed every year was way over-estimated, way, way, way over-estimated. So, you know, in the end, although it's –

one does have a very high risk of developing breast cancer if you have one of these mutations, the attributable risk is fairly small and the amount of breast cancer that it accounts for is fairly small. But that took a decade to figure out.

PC: This is the Breast Cancer gene 1 and 2, BRCA1 and BRCA2?

LF: Yeah, the BRCA1 and 2.

PC: One and two? Yeah.

LF: Yeah. So there was this idea that it would solve all of our problems in understanding breast cancer, but that hasn't – that has hardly happened. And after we did the breast cancer prevention trial, we did do the obligatory kind of, "Well, does it work in women that have mutation?" And we did do mutation sequencing for all of our cases of breast cancer. Dr. Mary-Claire King, who was the discoverer of the breast cancer gene did it, the bottom line being that it accounted for, I think, five cases of breast cancer in the entire study. And BRCA1 happens to be a non hormone-sensitive tumor usually, so Tamoxifen was probably not effective in that group. So what we thought was going to be the Holy Grail didn't exactly turn out that way.

PC: And when you followed up with the Star study, can you explain that and the relationship between that and drug companies for me?

LF: Yeah. So – so, the first Tamoxifen study, AstraZeneca, it was Zeneca at the time, was pretty gutsy. They only gave us drug and placebo. They didn't – I mean, that still amounted to a substantial amount of money. They did not pay for any of the trial, drug distribution or anything. But even, you know, making a statement by saying, "We'll allow our drug to be tested in a healthy population," was pretty gutsy. The subsequent, you know, congressional hearings, there was a fairly – there was something called the Women's Health Network, financed by Ralph Nader and his Citizens in the Public Interest – what is the –

PC: Yeah. Public Interest Research Groups.

LF: Yeah. Sidney Wolfson, Ralph Nader, that whole – anyway, there's a Women's Health Network that is part of that – Women's – I think that's what they're called. They were very much against the original Tamoxifen trials saying we were giving dangerous drugs to healthy women. And they engineered congressional hearings, which is when Bernadine Healy and Peter and I bonded sitting in front of a congressman for about five hours one day. [Laughter]. Any way, so the trial really took on a way more controversial life than it should have, and there were problems with data quality in another trial at NSABP, and Cong. John Dingell got involved, and we had to shut down everything for a couple of months, but eventually finished it. Astrazeneca got dragged in about side effects that Dingell decided weren't fully disclosed, although anyone that read the consent form would have seen that they were. We had to re-consent everybody. It was anything that you've ever, you know, read in history about what can go wrong with a clinical trial.

And, believe me, it was all – everything was run perfectly, but when you get congressmen involved, that's what happens. Lots of lawsuits and counter lawsuits.

And some people that got – let's just say Dr. Bernard Fisher, who ran the NSABP at the time, got many millions of dollars in settlements, so that to me is a testament to how we were right and all these people were wrong. But anyway, so when we finished the Tamoxifen trial, Tamoxifen reduced the risk (breast cancer in high risk women) by 50 percent, this other drug was coming along from Eli Lilly that had been approved for osteoporosis prevention, and appeared to be safer than Tamoxifen. There was some arm twisting because there was really nothing in it for Astrazeneca to put their drug up head to head with the Lilly drug, which we thought was going to be safer, but after some arm twisting, they agreed to. And it was also when the NIH was – when the NCI was pretty flush with money, it was during our doubling era, we had the mechanism set up, we had the machinery in place, and we just rolled from one trial into the other.

PC: Same, same group?

LF: Same group. Same network. And this time with some pages filled in in that empty book. [Laughter].

PC: Including the ones at the end, how to handle congress?

LF: Yeah, right [laughter]. At the same time, we had then, you know, also capitalized on our experience, and so we had our whole prostate prevention enterprise going.

PC: So these were running –

LF: Simultaneously.

PC: Simultaneously.

LF: Yeah, yeah. So I was a pretty busy person.

PC: Yeah. And the results of the Star?

LF: Were that, just what we anticipated. Tamoxifen and Raloxifene were equal in their breast prevention ability, but Raloxifene was – had less side effects, less uterine cancer, less thromboembolic events, but could only be used in post-menopausal women, and Tamoxifen was approved for pre and post.

PC: And so, by then, AstraZeneca –

LF: Well, AstraZeneca, they went to the FDA. They, in '98, got the first approval for a drug to reduce the risk of breast cancer. And then Eli Lilly went – I guess it was in 2007, they got Raloxifene approved for breast cancer risk reduction.

PC: Okay. And then the prostate cancer, did that run into problems as well, that study?

LF: So that one actually ran very smoothly. It was when we saw the results that – this is the power of editorial writers – the results showed that Finasteride reduced the risk of prostate cancer by 25 percent, which was what we were aiming for, that was the hypothesis but there was a 1.6 percent increase in high grade, what appeared to be high-grade tumors that were diagnosed in men on Finasteride. So less tumors overall, but higher number of tumors that were high grade. And that kind of drove the whole discussion that the editorial writer said it was only preventing non-significant tumors, and shouldn't – essentially said it shouldn't be used. And the company, this was Merck.

PC: Uh-huh.

LF: This happened within, let's see, the article was published in July, and over the summer there were discussions about, you know, should they go for FDA approval or not. This is also the drug they sold as Propecia for hair loss, so it had implications beyond just the prostate indication, prostate prevention indication. And by September, they were withdrawing Vioxx from the market because of unexpected cardiovascular toxicities, and there was no way they were going to risk anything, any other blockbuster products that they had before the FDA because of unanticipated side effects. So they, Merck didn't – I mean, this is my, my interpretation of the timeline, so they really had no interest in going

for a prostate prevention indication while the question of potential high-grade tumors was still around.

PC: And has –

LF: Subsequently, so that was 2003, 2004. Subsequently, we've done a lot more research on the tumors and the prostates, and re-reviewing every single slide, every single prostatectomy, and it appears that the explanation is – has more to do with bias related to Finasteride shrinking the prostate. And so if there is a high-grade tumor, you're more likely to hit it when you do a biopsy, than it is a real biologic phenomena. I mean, there have been, I think, three or four papers published just in the last six months, some modeling, some based on actual data comparing the pathology specimens that all come down to this conclusion. There's been talk again about should we go back to the FDA and try and get an indication.

PC: And then the other is the SELECT study (Selenium and Vitamin E Cancer Prevention Trial).

LF: Right.

PC: A little different. Tell me about –

LF: Yes. We started planning SELECT back in 2000. It went through – it was a very long planning period. I mean, the Finasteride study was totally accrued but not reported. And we were talking about what do we do next in prostate cancer, and we were faced with these two secondary analysis, one from the alpha-tocopherol trial that was done in Finland. That showed that Vitamin E appeared as – so we had, you know, those large beta carotene studies that showed that beta carotene increased the risk of lung cancer in smokers rather than the opposite effect. But in the Finland study, there was Vitamin E that appeared to decrease the risk of prostate cancer, and then there was another large selenium study done in Arizona, Clark was the P.I., that was directed at skin cancer, didn't decrease skin cancer but, again, showed a decrease in prostate cancer.

And plus a lot of animal data and other epidemiologic studies, and we went back and forth and decided that, you know, rather than pharmaceuticals, it probably would be – and since so many people take supplements, it would be nice to know what these supplements do. And after a very long gestational period, I think it was about three years of planning and discussion and expert committees, and what form of selenium and what dose of Vitamin E, we actually launched the study, which involved 35,000 men, which accrued in record time, in under three – I think just a little over three years we had planned for a five-year accrual period. We were pretty disappointed, I guess it's like three months ago now, four months ago, to hear from the data monitoring committee that there was absolutely no effect of any of the agents, and they recommended that we stop study supplementation.

PC: What took so long for the planning?

LF: Well, first, it was are these secondary hypotheses strong enough that we should launch something this big and this expensive. Then there was the – so selenium is selenium, but there's selenized yeast, there's selenomethionine. There's a number of different preparations that are sold as selenium, and there was a big question about which was the one that was the most bio-available, which was the one that could potentially be the most active, what did Clark use in his study? We had to go back and analyze his pills. So that was about, I'd say, a year process. There was also similar questions about Vitamin E. In the Finland study, it was 50 milligrams. We were proposing to use 400. Is that a safe dose? There were cardiovascular studies testing Vitamin E. The common wisdom was you needed to take it for cardiovascular health.

The question was: would we ever be able to maintain – continue the study once the results of the cardiovascular studies came out and Vitamin E, you know, was so wonderful and would be taken by everybody? As it turned out, it not only wasn't wonderful, it was detrimental in the cardiovascular study. So that problem got off the table. Then we had to make sure men knew that what they were taking wasn't going to harm them. But it just – it's, you know, when you're making an investment of $100 million and involving 35,000 men, there was, you know, writing the protocol, the peer review. So it just takes a long time. At one point, Dr. Coltman, who was the head of the Southwest Oncology Group that was sponsoring the study, we had one of our meetings with Selenium experts to come up with a consensus of what formulation we should use,

and the vote was split. He famously said, "I am not embarking on $100 million venture on a split vote." And so we, you know, kind of went back to the drawing boards and came up with a design that people could unanimously endorse. But that all takes time.

PC: Yeah, it does. Over the years, what changes would you tell me about in the division? What do you think are the significant changes?

LF: Well, some of the personnel changes, I think, were kind of in a detrimental sense. I mean, Ed Sondik was really one of the pillars of the division back in its early days. And during the whole – '94 during the, what we call the debacle, and Sam Broder subsequently leaving and Ed then became acting – NCI director, and then went to the National Center for Health Statistics, I think that was a major loss, both to the division and, probably, to the cancer community. I mean he was just such a good thinker. He wasn't trained in cancer. He was a biostatistician operations research person, but just a wonderful mind. And I think that hurt the division. If you go back even further, and Peter probably talked about this, I was not involved in that side of it, but our first deputy director was Joe Cullen. He was the architect of all of our smoking research or anti-smoking research. I think when he left, that was a blow to the division. That's some of the stuff that's now in Division of Cancer Control and Population Sciences.

PC: Uh-huh.

LF: And, you know, not to – I know I'm being taped, but Peter is – tends – his management style tends to – he's engaged at some times and not engaged at others. And that's kind of difficult over the years [laughter].

PC: [Laughter]. What accounts for the ebb and flow?

LF: I'm not sure. How well he's getting along with the NCI director [laughter].

PC: Well, that – yes.

LF: How many grandchildren he has [laughter].

PC: Well, I've certainly heard both stories.

LF: Yeah, right. I mean, we've always been, you know, this goes back to your first question about a prevention division in a traditionally treatment oriented environment, even if, you know, I say that cardiovascular and other places do prevention research, they don't really have divisions of prevention. And so we've always been somewhat of a stepchild. And, you know, really, Peter, when he came in the 80s, was building the field from absolute nothing, really from scratch. People thought of prevention as vaccines. We've come full circle now with the cervical vaccine, but back then, they didn't understand what it meant to reduce your risk or to prevent, you know, how could you possibly prevent cancer. So it's been a PR struggle, and it's, you know, we haven't always been the most popular kids

on the block. And I think since – actually, Harold Varmus and Rick Klaussner, I think, were very – they were very supportive, and they kind of put their money where their mouth was. They both – when we had the press conference to announce the results of the first breast prevention trial, they both came and spoke. David Satcher, who was the surgeon general at the time, at a congressional hearing, compared it to the discovery of small pox vaccine, you know, in terms of how really significant the findings were. Compare that to – fast forward to the Finasteride announcement, 25 percent reduction in prostate cancer, and our NCI director at the time, Andy von Eschenbach, "didn't like the trial," and refused to come or had a competing engagement when we had the press conference to announce those results.

PC: If Klausner was such a supporter, why did he split the –

LF: He was a supporter of the concept, but not the person. [Laughter]. Because Peter frustrated him.

PC: But not the conceptee, huh?

LF: Yeah. Because Peter frustrated him terribly.

PC: Okay. And relations with Varmus were better?

LF: I think so. Yeah.

PC: And what – what do you – would you say would be the great success of the division over the years? What would stick out in your mind?

LF: Well, certainly, the – well, all of the prevention trials, but the first one, I mean, to actually bring – you know, to get a drug approved for risk reduction in cancer. I mean, the greatest disappointment is that it hasn't been adopted more widely, and that's partly our fault for – the Cancer Institute, not mine, but the Cancer Institute's fault in not having a communications plan, and really the backbone to kind of go out there and promote the idea of cancer prevention. You know, when you hear about cancer prevention, you think of screening. So that would be one. And I really think the next generation of scientists that we've – that we've trained. I mean, this was – every cancer center now, whether they're functional or not, has a director of cancer prevention and control. And 20 years ago, that wasn't part of the cancer center criteria for comprehensiveness, and it just was given lip service, and now there are real research portfolios. M.D. Anderson has a huge cancer prevention building and the largest endowment of any of their programs. A physician that used to be here, Ernie Hawk, is the VP for cancer prevention at M.D. Anderson. I mean, those are huge statements about the viability of the field.

PC: And you said – I'm sorry, M.D. Anderson or N.D.?

LF: M.D. Anderson. The cancer center in Houston.

PC: Uh-huh.

LF: And other, other cancer centers have major cancer prevention programs. Probably the biggest disappointment has been that the pharmaceutical industry has not, has not bought into the concept. They haven't figured out that it actually could be profitable to develop drugs that could prevent cancer, like it's profitable to develop drugs that prevent heart disease.

PC: Uh-huh.

LF: And that's really been, you know, all these committees and suggestions about giving them extended patent life and stuff have not, have not kind of grabbed on in congress because congress, of course, has the mindset that drug companies charge too much and make too much money anyway. So it's hard to reconcile that with they won't – there's no incentive to develop drugs for prevention because it takes so long in the development process that by the time they're done, they're off patent. That's been a struggle.

PC: Uh-huh. Uh-huh. And the Tamoxifen and the Eli Lilly was –

LF: Yeah, they're – you know, the increase in sales based on their approvals hasn't been enough to spur the industry.

PC: Further, further work in the area.

LF: Yeah, yeah.

PC: And I would assume it's hard for a division to carry that water.

LF: Right. You know, we –

PC: As opposed to the whole NCI.

LF: Right. You know, we have, you know, an agent development group. We can develop agents and do small-scale studies, but you need pharmaceutical partners for any serious, you know, definitive Phase 3 trials.

PC: Uh-huh. Well, I want to thank you very much. Is there anything we haven't covered? Let me – that you'd like to talk about?

LF: I don't think so. I'm sure – you talked to Lori, right?

PC: Yes.

LF: You talked to Lori, and you talked to Eva, so they gave you – you did talk to Eva.

PC: No.

LF: No. Did you talk to anyone from the organ systems group?

PC: No. I don't think so. No. Let me look at my – the answer is, I'm pretty sure not.

LF: Okay.

PC: I talked to John. I talked to Barry Kramer, Vernon Steele…..

LF: Okay. So Vern does the agent development, the pre-clinical.

PC: Right. But no organ.

LF: Yeah. So I guess just to kind of fill in the one, the one missing piece, which is our early phase program so after I did all these large phase three trials, and we had a kind of – we had agent development, Vern's been in that group for a very long time, but we kind of had a missing link of how do we develop these agents in the smaller scale, phase one and two trials. And also, how do we develop organ expertise? And as a result of one of our retreats, we decided to reorganize into what we called the matrix organization. It never was really quite a matrix organization, but as a result, we did develop organ expertise in four organ site groups who would be responsible for the early phase research taking from pre-clinical into human studies. Any of the agents that became available, trying to capitalize on the molecular targets that were starting to emerge and the pathways so that

it was more than just taking from, you know, a secondary end point from a treatment trial and saying now we'll try it in prevention, but really trying to start earlier in the process, we know that this is the pathway that's involved, or the target of an agent. And so we develop these four organ systems groups, lung, GI, GU, prostate and breast and gynecologic cancers.

And I took over as kind of the associate director for clinical research, so I still oversaw that at a higher level, but also organizing the – these organ groups. And we developed a contract mechanism with six consortiums to do – paralleled after the Division of Cancer Treatment's program for doing early phase trials where these consortium would submit letters of intent to develop – do phase one and two trials, either solicited if they were agents that we had available or compounds, or ones that they could get, or were developing in their own centers. So that's kind of now one of the cornerstones of our prevention program is these consortiums. They're going to have to be re-competed in the next year or so, but they've, after some growing pains, have been fairly successful in doing early-stage biomarker endpoint studies, but points out again the lack of participation by the pharmaceutical industry in giving us agents to test.

PC: Uh-huh. So they're all done in the clinical centers.

LF: Yeah. So there are – we have contracts with Arizona, University of Arizona Cancer Center, Irvine, Northwestern, M.D. Anderson, I did say Mayo – Mayo Clinic in Rochester, and – you never remember all of them – oh, University of Wisconsin. And

they each have their own little networks. So it's been another way of kind of getting our tentacles out in the field. And it's – the enthusiasm and the camaraderie has really grown, I'd say over – this has been about five years that we've been in the field. So again, it's a matter of training a new generation of investigators of medical oncologists and others that are comfortable with the notion of cancer prevention research and really the concept that you can prevent cancer.

PC: Tell me about the retreats. Annual, semi-annual?

LF: Well, again, when we were flush, they were quite the affair. You know, we had entire division retreats at real retreat places out in – I guess if it wasn't West Virginia, it was close to West Virginia, and in Leesburg where we were wined and dined. They've gotten a little more minimal over the last two years. They would build camaraderie. We'd come out with all these plans, goals, mission statements, vision statements. Never – I'm not a big retreat and strategic planning type person, so probably a lot of it is my fault that there was a lot of enthusiasm and then things would kind of fall. The air was out of the balloon and business went kind of back to usual, but never quite as far back as before we had them.

PC: Uh-huh. And these are an annual thing?

LF: I guess they were – I mean it wasn't like, "It's time for our annual retreat," but probably the way it fell out, they were about annual.

PC: It's time to get together –

LF: Yeah.

PC: And sort of restart the engines.

LF: Yeah. And in the interim, we would have smaller retreats with just the leadership, the group chiefs. We haven't had a full division retreat in quite a while. We did have a leadership retreat last month.

PC: I wonder why they call it retreats when you really want to go forward.

LF: I know [laughter].

PC: Have to think about that one [laughter].

LF: Yeah.

PC: Well, thank you very much. I've enjoyed the conversation, and it's been very helpful.

LF: Okay. Good.

PC: And if I may, if I need additional information, okay to call you back?

LF: Oh, sure. Yeah. Absolutely.

PC: Terrific.

LF: Okay.

PC: Thank you.

LF: All right. Bye-bye.

PC: Bye.

[End of conversation.]