

Legends and Legacies Book Chapters

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Karen H. Lu, M.D.



**Professor of Gynecologic Oncology
H.E.B. Professorship in Cancer Research**



Karen tried on the cap and gown her mother wore to receive her master's degree.



Both Karen and husband Charles Lu, M.D., received medical degrees from Yale University School of Medicine in 1991.



Ned, 10, at left, and David, 14 can count on parents Charles and Karen, holding Kate, 2, to cheer for their various sports teams.

How I ended up where I am today is much clearer when examined in hindsight. Now, the choices I made that led me to my life's work as a gynecologic oncologist with a particular interest in hereditary cancers make sense. These choices were, in fact, not as random as they seemed at the time that each decision had to be made. Values that I hold and that were instilled in me — love of family, importance of the academic pursuit, joy of teaching — all guided those decisions.

I was born and raised in Baltimore, Maryland. My parents came from mainland China via Hong Kong to the United States to attend college and graduate school in the 1950s. Both came from scholarly families in China, and perhaps my commitment to academics comes from them. My paternal grandfather was a professor of chemistry who was educated at Johns Hopkins University. He was among a group of Chinese young men educated in the United States with scholarship funds established by the United States after the Boxer Rebellion. My maternal grandfather, a professor of economics, was educated in France. He later served as the head of China's legislature before the Communist regime, but I knew him only as the kind grandfather who played card games with me and gave me Juicy Fruit gum.

More recently, I have thought about the genetic link to my maternal grandmother. She was one of the first female graduates of Beijing University in the 1920s, where she majored in physics. Thereafter, she raised four children, served as a political wife, moved her family around China during the war in the early 1940s, and finally fled China for Hong Kong. I remember my mother telling me that while the rest of the family stayed in Hong Kong, my grandmother went to Malaysia by herself to teach college physics in order to support the family. Did she think about career goals? Did she worry about achieving the right balance of work and family life? Did she experience difficulties in academics because she was a woman? What I wouldn't give to be able to have a conversation with her now!

In contrast to my parents' and grandparents' dramatic lives, my childhood growing up in Baltimore was certainly less eventful. My immigrant parents believed that the route to success for their children in this new country was through education, so my brother and I went to traditional college prep schools in Baltimore (boys' school for him, girls' school for me). I loved attending an all-girls school because we were encouraged in every possible way. There was never any question that my classmates and I could achieve whatever we wanted to achieve, academically or otherwise. Contrary to the stereotype of Chinese parents, my parents never pushed me or my older brother academically, although I *do* think the ethic and value of scholarly pursuit was always present for us. We were both encouraged equally. The only time that my older brother felt any pressure from my dad was his gentle

encouragement of my brother to go to Johns Hopkins, since both my dad and grandfather had been students there. Since my brother chose to go there for his undergraduate studies and for his Ph.D., by the time I was deciding about colleges, the familial obligation had been fulfilled, and I headed north to Harvard.

In college, I was a biochemistry major; I chose that major partly because it led me to a smaller community within the university that was fairly nurturing. We had one-on-one tutorials with faculty and were required to do a project with a mentor that would lead to a thesis. I worked with David Williams, an M.D.-Ph.D. doing a pediatric hematology-oncology fellowship at Children's Hospital. He was from the Midwest and was smart, hard working and kind. Ultimately, what I valued from my experience with him was that he was an incredibly decent human being with equal passions for the research he was doing, for the pediatric cancer patients he was caring for and for his young family. I learned about the dedication that research involves (lots of weekends and nights with mice), and I learned about the value of scientific pursuit in medicine. Looking back now, it seems that experience must have influenced my decision to combine my own passions: for caring for women with gynecologic cancers, for translational research, and for my husband and three children.

One of my best experiences in college was meeting my future husband, Charlie. We grew up together in college and were great friends. We dated all through college, went our own ways for a few years, and then started dating again when we both were at Yale Medical School. When it was time to make decisions about matching for residencies, it seemed for us an easy decision to get married and enter into the "couples match." A "couples match" allows two people to merge their prospects together in the lottery that determines where medical students will do their residencies. It is a good test in negotiation and compromise for couples, and we had a relatively easy time deciding on our choices. By the time we got married at the end of medical school, Charlie and I had known each other for almost 10 years. I tell my sons that they need to really, *really* know someone before they get married, and I use our 10-year standard for their reference. I may have to revise my advice, but my point is this: having a long history with someone makes facing the challenges of life easier.

We ended up in Boston for residency — Charlie in Internal Medicine and me in Obstetrics and Gynecology. I loved residency. After all that coursework, this was the time when you really learned to be a doctor, and I loved all of it: delivering babies, surgery, clinic. My colleagues were fun, and the ones who weren't provided fodder for good humor. We worked like dogs, but it was easy to feel a sense of instant gratification. I do remember tough times of getting no sleep at night and then having to face a busy clinic

the next day. My motto for nights on call was: you had to sleep or you had to eat. If you couldn't do one, you had to do the other.

During the end of my second year of residency, I had to start thinking about whether to apply for a fellowship in one of the four subspecialties in obstetrics/gynecology. I definitely had a preference for subspecializing, as I didn't think that being a general obstetrics/gynecology physician, which usually meant private practice, fit me well. But what specialty? Urogynecology had interesting vaginal surgery, but I had a hard time getting passionate about urinary incontinence. The reproductive endocrinology and infertility attendings did interesting laparoscopic surgery, but I wasn't particularly passionate about infertility or endocrinology. That left gynecologic oncology. Not for the faint of heart, this field is unique in that it combines expertise in complex surgeries with expertise in chemotherapy. For a resident, this is one of the most exhausting yet most exhilarating and gratifying rotations. At the time, it was not the obvious choice for me, but, looking back, I cannot imagine a more suitable field. I am *passionate* about working with women who have gynecologic cancers.

The fellowship was three years, and, since my husband had started his medical oncology fellowship in Boston a year earlier, it made sense for me to remain in Boston for my fellowship, too. And as much as I enjoyed my residency, I enjoyed my fellowship more. The first year was a lab year, and I worked in Sam Mok's lab. Those in the field of ovarian cancer research know him for his accomplishments in understanding the molecular pathogenesis of disease. I had not thought seriously about lab work since college, but Sam brought out the latent molecular biologist in me. During that year, I understood the power of clinicians working with basic scientists. Sam had expertise, techniques and tissues to study ovarian cancer. Sam gave all new fellows in the lab a project that was already under way. After completing this initial project, we could start thinking about our own ideas for studies. This is what I loved. I could think of endless clinical scenarios in which having a molecular biology answer would really be helpful. Sam taught me the importance of having a tissue and serum bank. Because those resources were in place, I was able to ask and answer clinical questions using molecular biology and do it within a short period of time. Writing and submitting abstracts, assembling posters (back then, there was a lot more cutting and pasting), putting together PowerPoint presentations, and learning to write, re-write, and (again) re-write a manuscript are skills that I learned during my fellowship. You only have to do these things once or twice before the tasks become easier and less daunting. I can unequivocally state that my style of mentoring clinical gynecologic oncology fellows today derives directly from the way in which I learned from Sam and others during my fellowship.

It was also during my fellowship that I developed my interest in hereditary

cancer syndromes. BRCA1 and BRCA2 had recently been cloned, and there were plenty of clinical questions that needed answering. I remember during my clinical year taking care of a woman who was petrified that she would get ovarian cancer. Multiple women in her family had died of this disease, and she had recently found out that she carried a mutation in BRCA1. Although she was only in her mid-30s, we were going to remove her ovaries, and she was happy about it. Her surgery, done laparoscopically, was uneventful, and she went home the same day. A week later, we heard from the pathologist that both her ovaries and fallopian tubes showed microscopic pre-cancerous changes. But, unlike her female relatives, whose ovarian cancer had been diagnosed at stage 3 or 4 (when it is already widely disseminated, which is typically when it is diagnosed), she had her ovaries removed just as the cancerous process was beginning and, thus, was able to escape the fate of her female relatives. This experience made the power of the discovery of the BRCA1 and BRCA2 genes very real and vivid to me.

After spending 16 years in New England for college, medical school and training, I was hoping that we would move home to Baltimore for our first real jobs. Johns Hopkins and the National Cancer Institute (NCI) were obvious choices, so very early on (the end of my second year in fellowship), we approached our respective oncology departments there to ask about opportunities. However, it was entirely obvious, from a few phone calls and one interview, that neither was going to be a good fit for us.

Soon afterward, right before the start of my third year of fellowship, Charlie attended a meeting in Colorado and ran into a friend who had recently started work as an attending at M. D. Anderson Cancer Center in Houston. Was Charlie starting to look for a job? Would he like to have dinner with Dr. Waun Ki Hong the next evening? I remember the phone conversation with my husband after he had met with Dr. Hong — great job, great opportunity, great institution. Charlie flew down to Houston very soon afterward for an interview, and I began to pay attention when he came home and asked me if we could fax my resume to M. D. Anderson to see if there was a job opening in gynecologic oncology. From there, things progressed fairly quickly.

When Charlie went for his second interview, I went along. Although there was no formal job opening for me, at that time the department and program were expanding their translational research program in ovarian cancer. I had already secured funding from the American Gynecologic and Obstetric Society to do three years of translational research training. The enthusiasm of Charlie's three friends from Harvard was consistent and overwhelming: for junior faculty wanting academic opportunities, M. D. Anderson was *the* place to be. My lesson from this experience was this — start early to look for jobs in places that you really think you want to go. If it doesn't work, keep

an open mind. It is likely that the best opportunity may surprise you.

I remember one of my mentors in the fellowship program saying that you need to leave the institution where you trained so that you can grow up. If you stay, your attendings will see you as their trainee, and, worse, you will always feel like a trainee. I don't know whether that is always the case, but I *do* think it is good advice. It was healthy for me to leave Boston and my comfort zone. I learned that I could meet a new set of colleagues, find collaborators and mentors, figure out the way to a new operating room, and establish myself.

Two very fortunate events that occurred early in my career have defined the direction of my research and clinical interests. First, I came from my fellowship with an interest in hereditary cancers. A significant portion of my research as a fellow was devoted to ovarian cancer and BRCA1 and BRCA2. When I came to M. D. Anderson, I wanted to continue that interest but found out that there were fewer than 10 families with known mutations — not enough raw material to do any substantive research. I remember a chance encounter with Dr. Patrick Lynch, who led the registry for Hereditary Non-polyposis Colorectal Cancer (HNPCC), now referred to as Lynch syndrome. He said, “You know, we can never get any gynecologists to study Lynch syndrome.” What lay in front of me was a rich registry and expertise in a hereditary cancer syndrome in which women had an equal and significant risk of developing endometrial and colon cancer as well as a smaller but significant risk of ovarian cancer. I consider myself fortunate to have fallen into such an opportunity.

The second fortuitous event occurred when my colleague Dr. Russell Broaddus and I found out about a Request for Applications (RFA) from the NCI to conduct an endometrial cancer chemoprevention study in women with HNPCC. There had been very little studied on endometrial cancer and Lynch syndrome in general, but the goal was to examine two agents known to be effective in preventing endometrial cancer in the general population: oral contraceptives and progesterone. To really get a study like this done, two components would be necessary: 1) a registry of Lynch syndrome families from which to draw eligible women, and 2) knowledge of molecular biomarkers relevant to endometrial cancer that could be used as surrogate endpoints. I think we believed that this was something we *had* to do — where else was there such an established Lynch syndrome registry and investigators interested in endometrial cancer prevention? In addition, Russell knew a group at the UT Medical School that was studying the molecular effects of estrogen on post-menopausal endometrium in the context of hormone replacement therapy. Wouldn't it make sense to look at some of these same genes in endometrial cancer, which is believed to result from too much estrogen in the endometrium? There was a fantastic

opportunity to examine some of these novel genes as biomarkers. All the necessary pieces were in place to apply for this grant, but there was one catch. Neither of us had applied for this type of grant before, and the deadline was only four weeks away. I call this our “soup to nuts” grant submission. Russell and I had no expertise in putting together a budget or in assembling a consortium of other institutions, which required even more paperwork and more complicated budgeting. What we *did* have was youthful enthusiasm and help from Dr. Lynch’s team, which had recently completed a colon cancer chemoprevention study. We ended up getting the grant and gaining a lot of confidence along the way. This year, five years later, we completed accrual to this study. It took sheer force of will and a number of very dedicated individuals to complete this trial, and ours is one of the few, if not the only, gynecologic chemoprevention study for a hereditary cancer syndrome that has actually completed accrual.

The same youthful enthusiasm that went into this first grant re-surfaced when we began to consider submitting a uterine SPORE grant. I remember Russell, Mai Dinh (our project coordinator) and I meeting with one of our most respected mentors, Dr. George Stancel, who is dean of our UT Graduate School for Biomedical Sciences. We had lunch with him and proudly pronounced that we wanted to put a uterine SPORE grant together. He gave us really sound advice: don’t do it. I give full credit to Russell and Dr. Tom Burke for saying, “Let’s just try it anyway.” The deadline for submission only gave us eight weeks to focus on preparing the grant, but, frankly, after that chemoprevention grant went in, nothing seemed impossible. Because of Congressional budget delays, we didn’t find out until some 18 months after submission that the grant would be funded. By then, we just wanted the money and to get started with the research. My continued love for the research process has grown with the growth of the uterine cancer program, both at our institution and nationwide. Our success has been partly due to bringing in expertise from very different disciplines to focus on a cancer that has been really understudied. The other key to our success has been to encourage and draw in enthusiastic young scientists.

Looking back, I am surprised that I never considered the work-life balance more carefully as I made my career decisions. I chose what most would consider a time-intensive specialty because I liked it. Having children was a given, and we planned as best we could. In my third year of residency, I had a non-clinical six-week rotation, which I used for my first maternity leave. Our second child was supposed to come during my non-clinical year of fellowship, but perfect planning doesn’t always happen. Because I was a busy clinical fellow and because I wanted to honor a promise to my senior fellow that he could attend an important conference, I went back to work two weeks after my second son was born. I approached each of my maternity

leaves by taking extra call while pregnant, trading favors, and fulfilling my job when I returned from leave. It is a delicate balance to have children during medical training or even as an attending. I respected my colleagues and didn't want to ever feel that I wasn't pulling my weight.

As for that last child, I had been on staff for six years, had been promoted to associate professor, and at 41 was considered by the standards of my field to be of "advanced maternal age." We had finally cleared our house of all the baby paraphernalia, since our boys were 12 and 8. I tell people that we needed a shot of excitement into our well-balanced life. Our daughter has provided that, and, after so many years without an infant, she reminded me how difficult it is for working women to have babies. For us, what has always worked was having lots of help, including a live-in nanny and my parents, who take turns coming to Houston. Since my father is retired, he spends weeks at a time with us here. He drives the morning carpool for the boys and in the afternoon takes them to tennis, baseball or piano lessons. At their games and tournaments, he is their biggest fan. My mother still teaches, and she comes to visit and help out when she can. I know I could not be where I am today without their help. Besides my husband and parents, there are other key individuals who help make it possible for me to do the work that I do. All working women need to understand the value of their assistants; I know I would be nowhere without mine, Jeannette Upshaw.

I grew up with parents and teachers who assumed I would choose a life's work and pursue it passionately. Balancing the commitments of work *and* family is difficult. Thus, choosing what you do in life becomes that much more important. I believe that if you have a true passion for the things you choose to pursue, whether personal or professional, the rewards will be well worth the effort. So far, it's been that way for me.

