Second-guessing a second primary

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Education

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My story is one of a patient caught between the development of a new technology and its subsequent implementation in the clinical setting. My first breast cancer was diagnosed in mid-September 1994, in the same week that the *BRCA1* gene was located. The genetics of breast cancer had been in the news for several weeks and was of interest to me because of my family history of breast cancer. I was 46 years old and premenopausal when, on Sept. 23, 1994, I had a partial mastectomy with axillary node dissection that revealed a 1.5-cm invasive ductal carcinoma and 13 lymph nodes negative for metastases. Other encouraging prognostic factors were the absence of lymphatic, perineural or blood vessel invasion within the tumour, a low nuclear grade and estrogen receptors that were high-positive.

In accordance with the treatment guidelines of the British Columbia Cancer Agency and the fact that my tumour had been initially measured at 2 cm I was advised that I would need to undergo both radiation and chemotherapy in addition to surgery. However, when the excised tumour was smaller than expected my surgeon informed me that chemotherapy would not be necessary. I, on the other hand, wanted to begin the treatment. After spending several weeks wrapping my mind around the need for chemotherapy, I was not planning to go "gently into the night." I wanted to do everything possible to prevent any recurrences or further cancers. The oncologists I consulted at the British Columbia Cancer Agency several weeks later saw things differently; they did not consider me a candidate for chemotherapy.

Three weeks after the surgery I began to feel more like my old self, and I was less eager to infuse my body with therapeutic poisons. The medical oncologist easily convinced me that chemotherapy or tamoxifen would not be necessary in my case: "We have discussed the use of tamoxifen and I have not recommended it to [the patient] since the data that tamoxifen is suitable for low-risk patients is still not sufficiently strong to recommend it on a routine basis." The medical oncologist's report also included extremely relevant details about my family history, but they clearly were not considered in the development of my treatment plan. "Family history is interesting in that the patient's maternal grandfather developed carcinoma of the breast in his 30s to 40s and died of brain metastases. Her maternal aunt developed breast cancer in her 40s but is alive and well at 76. Of interest, the patient's paternal grandmother developed breast cancer in her early 70s." I had indicated that the same maternal aunt also developed malignant melanoma in her 30s, but this information was not included in the medical report.

The radiation oncologist agreed that my chances of doing well with surgery and radiation alone were excellent. Despite my "interesting" family history and the recent media attention devoted to *BRCA1*, genetic counselling or testing was never recommended to me.

Genetic counselling

Six months after my cancer was diagnosed I attended a lecture given by a medical geneticist on the genetics of breast cancer and the availability of genetic counselling at British Columbia's Children's Hospital. That was the first I had heard of the association between breast cancer in men and the *BRCA2* gene. I immediately wrote to the speaker, explaining my own crude pedigree of my family tree, and I received the first available appointment for genetic counselling — 6 months later. In retrospect, I was lucky to have waited only 6 months; waiting times of up to 8 months are not uncommon now.

As follow-up to the genetic counselling session, I requested and received the

medical records and pathology report for my maternal grandfather; he died at 43 years of age from a glioma. I discovered that he did not have a metastatic brain tumour, as I had originally thought, but another primary tumour. Both my grandfather and my aunt had more than one episode of primary cancer; this seemed important to the medical geneticist but was of little consequence to my oncology care providers. I later learned that multiple primary cancers in close family members is a risk factor for hereditary cancer. Because there was no interdisciplinary collaboration among my care providers, however, I am uncertain whether this information was ever conveyed back to the Cancer Agency.

Following my genetic counselling in October 1995 I was placed in the queue to wait for genetic testing; this technology did not become available in British Columbia until January 1997. The waiting time for genetic counselling and testing continued to grow. Only 1 part-time genetic counsellor could be supported with the seriously inadequate provincial funding, and families were prioritized for testing based on the number of family members affected. Consequently, I was still waiting in the queue when my second breast cancer (in the other breast) was diagnosed.

The second primary

In August 1997 I went for my annual mammograms and 3-year, semiannual oncology checkup with my radiation oncologist; all of the results seemed normal. There was, however, a suspected cyst in the right breast that could not be detected on a subsequent magnification-view mammogram. Based on my "low-risk" profile my oncologist suggested annual rather than semiannual follow-up visits. My surgeon continued to follow me semiannually, and in November 1997 he gave me a clean bill of health and an appointment to see him 6 months hence. I moved the appointment forward to April because of concerns about a painful ridge in my right breast that was only palpable in a non-breast-self-examination position (i.e., lying on my side), spontaneous discharge from the right nipple and a flattened (but not inverted or retracted) appearance of the right nipple.

A mammogram and the needle biopsy performed that same week proved "worrisome"; 3 ultrasound-guided core biopsies performed the next week revealed in situ carcinoma. I underwent a surgical biopsy the following week, which was actually a quadrantectomy because of the size of the tumour. A 2.4-cm invasive ductal carcinoma with lymphatic vessel invasion was removed just 3 weeks after my initial fine-needle aspiration. It was of intermediate grade and estrogen receptor positive. This "second primary" appeared shortly before my 50th birthday; I was still premenopausal. Bilateral breast cancer before the age of 50 is a red flag for genetic disease. It was now quite obvious that I was a prime candidate for genetic testing. A call to a genetic counsellor at the Cancer Agency quickly moved me to the front of the queue for DNA testing.

The aftermath

Ten days after my surgery, which included modified radical mastectomy on the right and a prophylactic total mastectomy on the left. A week after receiving my pathology report (4 of 17 lymph nodes were positive and a second small tumour was invading the dermis under the right nipple) I attended a hereditary cancer conference at the British Columbia Cancer Agency and learned of the criteria for referral to the Hereditary Cancer Program. Individuals whose family history includes at least 2 of 5 criteria are eligible for genetic-risk assessment. I realized, with alarm, that I met 4 of the 5 referral criteria — cancer in 2 or more closely related family members on the same side of the family, cancer at an earlier age than expected (e.g., breast cancer before menopause), multiple primary cancers in one individual, and a male in the family diagnosed with breast cancer. The fifth criterion was a family history of cancer associated with known hereditary syndromes (e.g., breast or ovarian cancer, or both). There was little opportunity for me to have a family history of ovarian cancer because my maternal grandfather had only 1 sibling, a brother, and my mother and maternal aunt both had complete hysterectomies in their 40s.

I have recently completed a 9-month course of treatment that included the mastectomies, 6 months of intensive chemotherapy with cyclophosphamide–epirubicin–flourouracil and 5 weeks of chest wall and axillary radiation. When I recover I will have prophylactic oophorectomies on the advice of a genetic counsellor at the University of Washington, as well as breast reconstruction. In the meantime I am participating in several genetic breast cancer studies and undergoing genetic testing at the British Columbia Cancer Agency. It will take up to 2 years to fully screen the *BRCA1* and *BRCA2* genes for possible mutations. Had my blood been drawn for DNA testing much earlier (i.e. when genetic testing first became available in January 1997) I might now have some information that could help my younger sisters and female cousins decide a course of action for themselves.

Agonizing questions that awaken me in the middle of the night

In the fall of 1997 I was featured in a story in the British Columbia Cancer Agency's millennium campaign newsletter about my emerging profile as a breast cancer researcher. I expressed great confidence in the standardized guidelines that guided my treatments during both episodes of breast cancer. "I discovered [that] if you have to have breast cancer, this is a good province to have it in. As a researcher I respect the British Columbia Cancer Agency's treatment guidelines because they are based on evidence." Unfortunately for me, and perhaps for others, the rapidly emerging genetic evidence has not been factored into the treatment guidelines yet.

The questions that wake me up on far too many nights: "Could this second breast cancer have been prevented?" How did I fall between the cracks? Why was there no interdisciplinary collaboration among the oncologists, the surgeon and the medical geneticist? Why were the obvious genetic implications of my family history not considered during my first experience with breast cancer? With a family history of 2 close relatives who had multiple primary cancers before 50 years of age, one of whom was a man with breast cancer, why didn't this pedigree scream out for the need for genetic testing and raise the profound possibility that I might develop a second primary cancer? Was it prudent for the medical oncologist to recommend against taking tamoxifen in 1994? Could it have prevented the second, far more serious breast cancer? In light of my family history should I have been advised to have bilateral mastectomies following the first episode?

I have placed enormous trust and faith in my oncology care team during the past 5 years. To say that my confidence has been eroded would be an understatement. I believe that had I been followed by an interdisciplinary team in which there was collaboration my scenario might have played out quite differently.

My prognosis now is not nearly as promising as it was after the first diagnosis. Even with the widely touted success of the chemotherapy I underwent this past year, I have nearly a 1-in-3 chance of dying by the age of 55 and a 1-in-2 chance of a recurrence by that age. These are the odds that wake me up in the middle of the night. These are the odds that I wish could have been prevented.

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