



# Are bilateral cancers hereditary? Part II

*A Countercurrents Series<sup>a</sup> with  
S.A. Narod MD*

There is no disputing that cancer susceptibility genes, when mutated, may give rise to bilateral cancers in those who inherit a mutation. But is it equally true that all bilateral cancers have a hereditary origin—that is, are they all caused by an inherited germline mutation?

Inheritance was the prevailing wisdom in 1989, when I was a fellow at the International Agency for Research on Cancer in Lyon, France, in their Programme of Viral and Hereditary Factors in Carcinogenesis (neither factor being considered of sufficient importance at the time to merit its own program), under the guidance of Gilbert Lenoir. After taking a hard look at the available data, we decided that the prevailing hypothesis was probably not the case. The crux of the argument was that familial Wilms tumours were not more likely to be bilateral than sporadic (non-familial) Wilms tumours were. In June 1991, we published a short article in the *International Journal of Cancer* with the provocative title “Are Bilateral Tumours Hereditary?”<sup>1</sup>. The article turned out to be less provocative than I had anticipated; it was more or less ignored. In the 20 years that have since elapsed, it has been cited 10 times (9 if you omit self-citation)—the last time in 1995. Perhaps people did not believe us, or perhaps the topic was considered to be unimportant. I prefer to think that it somehow slipped under the radar.

Undoubtedly, some bilateral cases are hereditary. The classic example is retinoblastoma: If a child is diagnosed with bilateral retinoblastoma, then in all likelihood, that child carries a mutation in *Rb1*, and should he or she have offspring, the likelihood of passing the mutation on is 50%<sup>2</sup>. Other examples of hereditary bilateral tumours are those of the thyroid or adrenals in multiple endocrine neoplasia syndromes, acoustic neuromas in neurofibromatosis type 2, and kidney tumour in von Hippel–Lindau disease.

The retinoblastoma data were correctly interpreted by Alfred Knudson and were the basis for his formulation of the two-hit hypothesis<sup>2</sup>, but he then went out on a limb with Louise Strong and tried to extend the model to other childhood cancers, including Wilms tumour<sup>3</sup> and neuroblastoma<sup>4</sup>, for which the evidence was scanty.

A third example that does not comply with the hypothesis that bilateral cancers are hereditary is that of testicular cancer. This cancer is sometimes associated with birth defects (cryptorchidism, hypospadias), but rarely with a family history of the same type of cancer. In any case, if bilateral childhood cancers are hereditary, then the relevant genes should have been found by now; the time (and money) have been ample. Until the genes are discovered, I shall remain a skeptic.

If bilateral cancers are not genetic, then what are the alternative explanations?

Some might be a result of chance. For example, if the risk of contralateral cancer is 10 times the expected level, then about 1 in 10 bilateral cancers should be the result of chance. Epidemiologists think that a common environment is involved. Genetic epidemiologists think that multiple genes with small effects—that is, single-nucleotide polymorphisms—are the cause. But environmental or genetic factors have yet to be found.

An alternative explanation (and one that is the hardest to test) is that these three cancer types are the result of abnormal cell development and that there are populations of cells with a tendency to develop cancers. In some cases, an association between a pediatric cancer and the presence of one or more congenital malformations is noticeable<sup>5</sup>. In the case of neuroblastoma, an excess of cardiac malformations is seen<sup>6</sup>. Children with Wilms tumour may have one of several different malformations, most commonly a malformation of the urogenital system<sup>5</sup>.

The most interesting example is the origin of bilateral breast cancers. Some are no doubt attributable to *BRCA1*, *BRCA2*, or *CHEK2*, but fewer than 10% of women with bilateral breast cancer carry a mutation.

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Not a lot of data has been generated on the heritability of bilateral breast cancers. It would be of interest to compare the risk for breast cancer in the daughters of women with bilateral and unilateral breast cancer, matched for age of first cancer. A risk higher than expected would argue for a heritable cause. A risk that is similar would suggest a need to look elsewhere.

The most puzzling question raised by the descriptive epidemiology of bilateral breast cancers is why they are so frequently concordant for estrogen receptor (ER) status or other markers<sup>7,8</sup>. In the recent past, I have argued in favour of a hypothesis that the relative size of breast stem cell populations may predict cancer risk<sup>9</sup>. If that argument were to be extended to include two different predominant normal stem-cell populations, one of which confers risk for ER-positive breast cancers and one of which confers risk for ER-negative breast cancers, it might help to explain the similarity between the breasts. The assumption would have to be that the concentration of stem cells is similar in the two breasts and that those populations are predominantly of either the ER-positive or ER-negative precursor types. The trick is how to find them.

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**Correspondence to:** Steven A. Narod, Women's College Research Institute, Women's College Hospital, and the Dalla Lana School of Public Health, University of Toronto, 790 Bay Street, Toronto, Ontario M5G 1N8.

**E-mail:** steven.narod@wchospital.ca