Earlier age of onset in *BRCA* carriers—anticipation or cohort effect?

A Countercurrents Series[a] *with S.A. Narod* MD

Is the age of onset of breast cancer in women with a *BRCA1* or *BRCA2* mutation decreasing?

Two recent papers suggested that the effect of mutations is more profound with each successive generation [1,2]. In a paper from Spain, the average age of breast cancer diagnosis declined by 6.8 years in *BRCA1* carriers and by 12.1 years in *BRCA2* carriers in one generation [1]. In Texas, the median age of diagnosis declined by 6 years in a single generation, from 48 to 42 years [2]. To be fair to others, the same phenomenon has been reported many times, dating back to 1993 [3–10].

What could be the cause of such an abrupt shift? Perhaps a deteriorating environment coupled with widespread inactivity among women? Perhaps women are being better screened? Or is the nature of the mutation changing?

In each study, the authors reviewed the pedigrees of families with a *BRCA* mutation where women were affected both in the current ("proband") generation and in the parental generation. The average age of diagnosis in each generation was calculated, compared, and found to be younger in the proband generation. But before examining those studies in detail, it is important to distinguish between genetic anticipation and a cohort effect.

"Anticipation" refers to penetrance that increases with the number of generations elapsed since the mutation first arose *de novo* in a single individual. Anticipation was proposed for retinoblastoma (for which no molecular mechanism has been identified) in the 1970s [11], but better-known examples are Huntington disease [12] and myotonic dystrophy [13] (for which dynamic mutations in trinucleotide repeats underlie the shifts). It is important to note that, in anticipation, a decline in age at diagnosis is observed with subsequent generations *within a pedigree,* but the average age of diagnosis in the population shows no change with calendar time because each generation contains a mix of first-generation carriers, second-generation carriers, and so on. It is believed that, eventually, the age of onset becomes young enough that reproductive fitness is impaired, and the most harmful alleles are thereby lost in the population (and are replenished by *de novo* mutations).

In a cohort effect, penetrance of the gene depends on the year of birth of the carriers. When a cohort effect is present, a decline in age at diagnosis with subsequent generations within a pedigree is also observed, but the average age at diagnosis in the underlying population is also observed to decline with calendar time, and the age-specific incidence rates are seen to increase with calendar time. Age-specific rates of cancer might also decline with age in a cross-sectional study.

The groups from Spain and Texas both invoked anticipation as the likely mechanism for the observed declines in age of onset from generation to generation. But consider the most common *BRCA1* mutation, 5382insC. This mutation has been estimated to have arisen some 70 generations ago somewhere in Eastern Europe [14]. Does that provenance mean that the average age of diagnosis has been creeping down for each of 70 generations? Or only for the last one, like a dormant volcano that suddenly becomes active? Or is it the case that genetic anticipation acts on Houston mutations, but not on 5382insC mutations?

Neither explanation will do. A cohort effect seems much more likely. Problems are inherent in both the Spanish and the Texas studies. Consider two hypothetical nuclear pedigrees: In each family, the mother is 75 and the daughter is 50. In the first family, the mother developed breast cancer at age 60, and the daughter developed breast cancer at age 40. In the second family, the mother developed breast cancer at age 40, and the daughter, healthy at 50, develops breast cancer 10 years later at age 60. In theory, these families should cancel each other out, but only the first family is eligible for the study. A woman in the first generation may have had breast cancer at any age up to 70, but a woman in the proband's generation can only have early-onset breast cancer. Furthermore, it is

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critical to consider the criteria for genetic testing. If a young patient is more likely than an elderly patient to be tested, then the proband's generation will be enriched for early-onset breast cancer. This analysis is pertinent for hospital clinics in which an early age of diagnosis is an explicit testing criterion. Lastly, the proband's generation will include only *bona fide* carriers. The mother's generation will include affected women who have not been tested and may include sporadic cases diagnosed, on average, at older ages.

But better studies also support the idea of a cohort effect. One design that does not suffer from ascertainment bias involves studying a large and unselected series of breast cancer cases to identify the *BRCA*-positive subset, subsequently comparing the lifetime cancer risks in the sisters and mothers. If a cohort effect is present, then the lifetime risk of cancer should be greater in the sisters than in the mothers. Studies of this kind, with the results expected for a cohort effect, have been conducted by Gronwald *et al.* [8] in Poland and by King *et al.* [7] in the United States. The breast cancer risk by age 50 was estimated by King and colleagues to be 24% among mutation carriers born before 1940, but to be 67% among those born after 1940.

Another approach is to show that the prevalence of *BRCA1/2* mutations among incident cases of breast cancer increases with time [14]. The assumption here is that the prevalence of mutations in the underlying population is fixed and that the risk of nonhereditary cancer does not change over the study period. In a prospective study of carriers in North America, we recently showed that the annual cancer rate was highest among women aged 25 to 40 years [15] (Table I). For young women, the annual risk reached an astonishing rate of 38% over a 10-year period—almost 4% per year. This effect may be age-related (that is, the cancer risk declines with age), but a cohort effect is also possible: that is, the risk for women born during 1935–1950 is about 1% per year throughout their lives, but the risk for women born during 1970–1985 is almost 4% per year. Either way, the enormous risks that young women with a mutation now face are a matter of concern. It is important that proper epidemiology studies be conducted so that the factors contributing to this risk—and to possible risk increase—can be identified.

TABLE I Annual rates of breast cancer in carriers of *BRCA1* mutations in North America[a]

	Age cohort (years)			
	25–39.9	*40–49.9*	*50–59.9*	*60–75*
Cancers (*n*)	20	28	18	5
Person–years (*n*)	521.5	1031.0	839.1	583.5
Annual rate (%)	3.8	2.7	2.1	0.9

[a] Adapted from Lubinski *et al.* [15]

CONFLICT OF INTEREST DISCLOSURES

The author has no financial conflicts of interest to declare.

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