Sir,

Retinoblastoma (Rb) is the most common primary malignant intraocular tumour in childhood, with an incidence of 1 in 15,000 live births. It essentially affects the retina of young children under the age of five years, and may involve one eye (unilateral retinoblastoma) or both (bilateral retinoblastoma). Retinoblastoma is commonly reported to be sporadic in 60% of cases and hereditary in the remaining 40%.

In 1971, Alfred G. Knudson Jr., based on the observation of 48 cases and published reports developed a hypothesis according to which this eye cancer is caused by two mutational events (“two hit hypothesis”) [1]. According to this hypothesis, in the dominantly inherited form of the disease, one mutation is inherited via the germinal cells and the second spontaneously occurs in somatic cells of the retina and other tissues of the body. On the contrary, in the non-hereditary form, both mutations will occur in the somatic (retinal) cells. The “two hit” theory led to the discovery of the so-called tumour suppressor genes and the identification of the Rb1 as the prototype of such genes. Mutations of the Rb1 gene are now commonly believed to be the “cause” retinoblastoma and during the last three decades or more, little or no doubt has been cast by scientists worldwide on this undemonstrated belief.

Although the “two hit” theory is still largely used to explain the genesis of retinoblastoma, it makes predictions which are not fulfilled by the clinical and epidemiological evidences; among others:

(1) Bilateral retinoblastoma is diagnosed earlier (mean age = 15 months) than unilateral (mean age at diagnosis = 24 months);

(2) Sporadic, hereditary and familial retinoblastoma, all depend on one and the same process, i.e.: the loss or inactivation, through mutation, of both copies of the Rb1 gene;

(3) All bilateral cases (25–30%) should be counted as hereditary because the proportion of affected offspring closely approximates the 50% expected with dominant inheritance;

(4) Familial retinoblastoma with the unilateral disease phenotype accounts for no more than 1–1.5% of all cases;

(5) Retinoblastoma is “caused” by mutations affecting the Rb1 gene.

As we have shown elsewhere [2,3]:

– Prediction (1) derives from the inappropriate use of the “mean” for calculating the age at diagnosis of both unilateral and bilateral retinoblastoma, being the bilateral cases diagnosed within the first 36 months of life, and the unilateral ones “spread” over a much wider age range, encompassing the ages of 17, 40 and 45 years in our series of 387 retinoblastoma patients. Meta analyses on larger series confirm that the vast majority of both unilateral and bilateral cases, are diagnosed within the first 24 months of life.

– Prediction (2) is contradicted by the common sense and data showing that there is a significant difference in the world incidence of unilateral (sporadic) retinoblastoma, among different countries, clearly indicating that, unlike the bilateral (hereditary) form of the disease, unilateral retinoblastoma may be caused by environmental factors, including poor diet, and infectious agents.

– Prediction (3) does not take into any consideration the fact that in a large number of bilateral cases, no mutations can be found (sporadic bilateral retinoblastoma) even with the most advanced molecular techniques. Moreover, personal series of retinoblastoma survivors (unpublished data), clearly show that this prediction applies to unilateral retinoblastoma too with 50% affected children in the offspring of unilateral retinoblastoma survivors.

– Prediction (4) is contradicted by the epidemiological data, showing that the incidence of the unilateral...
eral disease phenotype, among the familial cases of retinoblastoma, is much higher (24–28%) than that reported for hereditary retinoblastoma.

– Prediction (5) does not take in any consideration that:

(i) the Rb1 gene pathway is compromised in almost any type of cancer;
(ii) it is not the only pathway involved in either retinoblastoma or cancer in general;
(iii) it is strictly linked to aneuploidy;
(iv) aneuploidy itself seems to drive cancerous transformation;
(v) epigenetic mechanisms (gene “silencing”, methylation, histone acetylation, genomic imprinting) may be involved in the genesis of retinoblastoma.

Overall, in the light of epidemiological, clinical, and more recent biological and genetic evidences, the “two hit” theory represents a rather simplistic, outdated, and unreliable model to explain tumour development and clinical evolution of retinoblastoma.

References

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