Quantitative Estimation of Chromosome Aberration Frequency in Cancer Patients Induced by Endogenous and Exogenous Factors

A. N. Chebotarev, O. P. Kirichenko,* and O. I. Sokolova*

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 130, No. 11, pp. 574-576, November, 2000
Original article submitted July 13, 2000

In patients with skin melanoma and colon cancer, cell distribution by the number of chromosome aberrations cannot be described by Poisson distribution, but corresponds to a bipopulation model combining the Poisson and geometric distributions. In contrast to the control, in patients with malignant tumors, cells with geometric distribution possess the majority of chromosomal aberrations.

Key words: *melanoma; colon cancer; chromosomal aberrations; distribution*

Multiaberrant (rogue) cells were discovered long time ago, but now the interests of many explorers are focused on the appearance of these cells. These cells were most frequently observed during total examinations of the frequency of chromosomal aberrations in population suffered from Chernobyl accident [2,3,7]. However, cells with multiple aberrations were also found in other population groups [1,9]. It was assumed that these cells participate in mutagenesis, teratogenesis, and oncogenesis [9].

Bipopulation model based on the idea of existence of two cell populations was proposed for quantification of rouge cells. Judjing by the number of aberrations, most cells show the Poisson distribution. These chromosome aberrations are caused by external mutagenic factors. In the other smaller cell population aberrations show geometric distribution. It is assumed that this distribution results from mutations in genes responsible for reparation and replication. Mutations of these genes cause aberrations in other genome loci. This model allows to explain the appearance of multiaberrant cells in subjects living in ecologically unfavourable regions [6].

Medical Genetic Research Center; *N. N. Blokhin Russian Cancer Research Center, Russian Academy of Medical Sciences, Moscow

Chromosome instability associated with the risk of tumor development is known to accompany some rare autosomal recessive syndromes [8]. In the present study we applied the bipopulation model for description of cell distribution by the number of aberrations in patients with two tumor types (skin melanoma and rectal cancer) and analyzed the contribution of each subpopulation to the total number of aberrations.

MATERIALS AND METHODS

The frequency of chromosomal aberrations in peripheral lymphocytes was examined in patients with skin melanoma or colon cancer. Healthy donors living in Moscow comprised the control group. The methods of cell culturing, fixation, staining, and analysis of preparations were described earlier [4].

The parameters of the model were determined by the formula for the number of cells with z aberrations:

$$T(z)=T[(1-a)\times\exp(-z)\times m^z/z!=a\times t\times(1-t)^z, \quad (1)$$

where T is the total number of analyzed cells; a is the number of cells with geometric distribution by the number of aberrations; m is the Poisson distribution parameter (mean number of aberrations per cell for cells with Poisson distribution); t is geometric distri-

0007-4888/00/0011-1106$25.00 ©2000 Plenum Publishing Corporation

bution parameter (fraction of aberration-free cells in cell population with geometric distribution); z is the number of aberrations per cell; $T(z)$ is the number of cells with z aberrations. The values of parameters were calculated using the sum of minimal square deviations between measured and expected values.

RESULTS

The number of aberrant cells in patients with melanoma did not differ from the control (χ^2=2.17; df=1; p=0.14), while in patients with colon cancer it increased significantly (χ^2=8.56; df=1; p=0.0034). In both cases cell distribution by the number of aberrations did not correspond to Poisson distribution (p<0.05). At the same time, the expected numbers of aberrant cells calculated according to the proposed model agree with the experimental data in all groups (p>0.05; Table 1). These results confirm previous data on inadequacy of Poisson distribution to cell distribution by the number of chromosome aberrations in subjects living in ecologically unfavourable regions [1].

The first item in formula (1) describes the formation of aberrations due to external mutagenic factors and these cells are distributed according to Poisson distribution. In the control group this distribution is typical of 99% cells, while in melanoma and colon cancer these numbers decrease to 86 and 82%, respectively. The number of aberrations per cell is not high and varies from 0.021 to 0.035 (m parameter).

The second item of formula (1) describes the cells with geometric distribution by the number of chromosomal aberrations. This population is characterized by the presence of rouge cells. The formula $M=(1-t)/t$ establishes the relationship between t and the mean of geometric distribution [5] and allows to calculate the mean number of aberrations per cell for this population, which 10-fold surpasses that for the population with Poisson distribution (0.267-1.370 aberrations per cell). Formula (1) allows to calculate the number of aberrations in both cell subpopulations. In the control, 75% aberrations develop due to occasional effects of mutagenic factors and correspond to Poisson distribution (Table 2). At the same time, in both groups of cancer patients the major fraction of aberrations develops in cell population with geometric distribution.

Thus, the obtained data show that most chromosomal aberrations in patients with melanoma and colon cancer are determined by the effect of endogenous factors. The number of cells with geometric distribution by the number of aberrations significantly increased. Rouge cells can occur in this subpopulation. The analysis of cell distribution by the number of aberrations allows to evaluate the number of these cells and the number of chromosome aberrations, which

TABLE 1. Measured and Expected Distribution of Cells by the Number of Aberrations in Healthy Donors and Patients with Skin Melanoma and Colon Cancer

Group, distribution	Number of cells with aberrations								χ^2	Degree of freedom	Probability
	0	1	2	3	4	5	6	7			
Control (n=22, 1690 cells)	1625	60	3	0	0	1	0	1			
Poisson distribution	1613.77	74.48				1.75			8.93	1	0.0028
model distribution	1625.08	60.1	2.62			0.94			1.25	1	0.26
Melanoma (n=32, 3410 cells)	3248	140	17	3	1	0	1	0			
Poisson distribution	3222.36	182.38				5.26			63.33	1	1.89×10^{-15}
model distribution	3248.21	140.21	17.17	3.48		0.93			1.30	1	0.25
Colon cancer (n=20, 2000 cells)	1881	101	14	3	0	1	0	0			
Poisson distribution	1862.07	133.13				4.87			43.35	1	4.68×10^{-11}
model distribution	1881.07	101.07	14.08	2.96		0.82			0.041	1	0.84

TABLE 2. Model Parameters and Quantitative Characteristics of the Frequency of Chromosomal Aberrations in Three Groups of Subjects

Model parameters	Control	Melanoma	Colon cancer
% aberrant cells	3.85	4.75	5.95
Aberrations/cell	0.0462	0.0566	0.0715
Number of aberrations per cell in population with Poisson distribution (m)	0.035	0.021	0.024
Fraction of aberration-free cells in population with geometric distribution (t)	0.423	0.790	0.783
Fraction of cells with geometric distribution (a)	0.0067	0.138	0.185
Number of aberrations per cell in population with geometric distribution $M=(1-t)/t$	1.37	0.267	0.277
Fraction of aberrations in cells with geometric distribution, %	23.88	67.31	72.58

necessitates the need of estimation of the total number of aberrations and their distribution in cells.

The study was partly supported by the Russian Foundation for Basic Research (grant No. 98-04-49041).

REFERENCES

1. N. P. Bochkov, N. A. Popova, L. D. Katosova, *et al., Genetika*, **35**, No. 5, 735-742 (1999).
2. E. V. Domracheva, S. A. Kuznetsov, E. N. Shklovskii-Kordi, and A. I. Vorob'ev, *Gematol. Transfuziol.*, No. 11, 36-37 (1991).
3. M. A. Pilinskaya, M. M. Shemetun, S. S. Dybskii, *et al., Tsitol. Genetika*, **28**, No. 1, 27-32 (1994).
4. O. I. Sokova, O. P. Kirichenko, O. E. Kulagina, *et al., Genetika*, **33**, No. 9, 1297-1302 (1997).
5. G. Korn and T. Korn, *Mathematics Handbook for Researchers and Engineers*, Moscow (1968).
6. A. N. Chebotarev, *Dokl. Ros. Akad. Nauk*, **371**, No. 6, 847-849 (2000).
7. A. V. Sevan'kaev, A. F. Tsyb., D. C. Lloyd, *et al., Int. J. Radiat. Biol.*, **63**, No. 3, 361-367 (1993).
8. S. Heim and F. Mitelman, *Cancer Cytogenetics*, N.Y. (1995).
9. J. V. Neel, A. A. Awa, Y. Kodama, *et al., Proc. Natl. Acad. Sci. USA*, **89**, 6973-6977 (1992).