A SIMULATION OF THE FORMATION OF MELANOCYTIC NEVI

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Abstract

Melanocytic nevi (moles) are common, and can be found anywhere on the skin. Their number has been shown to be associated with a greater risk of cutaneous melanoma. Also, the knowledge of their natural evolution is important in the understanding of the development of melanoma. The aim of this study was to incorporate available knowledge about melanocytic proliferation and the role of immune system and to create a simulation model which will be able to explain the changes in number of melanocytic nevi during lifetime and to elucidate the importance of the immune system in their formation and regression (i.e. eruptive benign melanocytic nevi). The results were presented graphically and visually analyzed. Because of the great number of possible numerical solutions only approximately results that satisfy some basic criteria were take into account. A created system dynamics model proved to be able to simulate the appearance and disappearance of melanocytic nevi during lifetime and the eruption of nevi after immunosuppression in a way that mimics their changes reported in epidemiological studies. There are limitations in model assumptions due to many uncertainties regarding model parameters and thus much more detailed epidemiological data would be required for the creation of a more reliable model.

Keywords: Melanocytic nevi, Mutation, Immune system, Simulation model, System dynamics

Presenting Author's biography

Jadranka Božikov graduated in Mathematics and earned MSc and PhD degree in field of Biomedicine and Health Sciences at Zagreb University. Since 1978 she works in Department for Medical Statistics, Epidemiology and Medical Informatics at Andrija Štampar School of Public Health, Medical School, University of Zagreb, currently as associated professor. She introduced simulation modeling methods and applications as teaching subject for medical students and graduates and supervised several MSc theses obtained by young researchers who employed system dynamics approach and continuous simulation techniques in their investigation of the phenomena in medicine and public health. URL: www.snz.hr/~jbozikov.

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1 Introduction

The incidence of cutaneous melanoma has increased dramatically during the past several decades (1). The presence of multiple nevi has been shown to be associated with a greater risk of cutaneous melanoma (roughly 2 to 14 fold) [1,2]. Melanocytic nevi (moles) are common, and can be found anywhere on the skin. An acquired melanocytic nevus is a benign proliferation of cells with melanocyte differentiation [2]. From the same cells melanoma arises. That's why knowledge of the natural evolution of benign nevi is important in the understanding of the development of melanoma [3]. Whether nevi are precursors of melanoma or simply markers for innate susceptibility to melanocytic proliferation remains an issue of debate, but the number of melanocytic nevi is still a risk marker for cutaneous melanoma. While twin studies suggest that the number of melanocytic nevi is a characteristic under genetic control, at the same time there is epidemiological evidence that their number is influenced by environmental factors [4]. Their evolution is a dynamic process with moderate degree of turnover (during life many nevi appear and disappear) [3]. Also, melanocytic nevi may appear suddenly (eruptive benign melanocytic nevi) or become more prominent in response to sun exposure, immunosuppression and other factors. The pathophysiology of eruptive benign melanocytic nevi is unknown, although different hypotheses have been stated. One of the most plausible theories that may account for their formation asserts that the intact immune system inhibits the proliferation of melanocytic lesions [5]. Also, in some cases the regression of nevi is caused by the immune system (halo nevi) [6]. Mathematically, a single mutation can be at the base of the formation of melanocytic nevi, with a probability of mutation per cell per mitosis between 10^{-9} and 10^{-7} [7]. The number and size of nevi during lifetime is not definitely and with certainty established, but roughly their number increase during the two first decades, reaching the maximum during the second and third decade, and after that their number diminishes [1-4, 7-12].

2 Aim

The aim was to crate a conceptual and simulation model that can explain the number of melanocytic nevi during lifetime, based on known data and hypotheses, and to determine the possible importance of the immune system in their formation and regression.

3 Material and methods

Data reporting number of nevi at different age and theoretical number of mutations in melanocytes were collected from different articles. Hypotheses and theories about the formation and regression of melanocytic nevi were synthesized to create the conceptual model. Based on that model a rough simulation model was created.

Stella Research v.8, a program for dynamical simulation, was used for modeling and simulation [13]. To determine the best values for the model's parameters (immune suppression of the growth of nevi, probability of mutation in melanocytes, death of nevomelanocytes) a series of simulation experiments were conducted. Mutations per cell per mitosis was based on published data and set between 10^{-9} and 10^{-7} with a step of 10^{-9}. The influence of the immune system on the nevus growth and the probability of death of nevus cells and nevi was set between 0 and 1 (0-100% probability per time unit - year) with a step of 0.01. The results were represented graphically and visually analyzed. The criteria to accept the values of the number of mutations per cell per mitosis were the formation of approximately 20 nevomelanocytes (nevus cells). The minimal criteria to accept the results of the entire model as credible/possible were: 1) an increase of the number of nevi during the first two decade of life, 2) at least 20 nevi in the second or third decade of life and 3) their gradual disappearance after that (Fig.1).

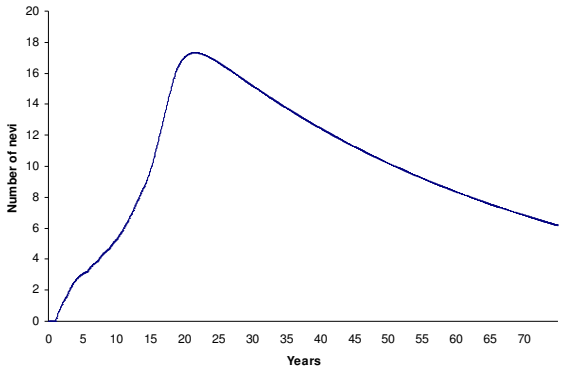

Fig. 1 An approximate curve of the number of nevi during lifetime.

4 Results

The model was conceived in two main parts (Fig. 2): 1. modeling of the number of mitoses to create approximately $2 \cdot 10^8$ melanocytes in the skin in an adult person, 2. disappearance of nevomelanocytes (in the model single nevomelanocytes was called Nevus cells), regression of melanocytic nevi and the influence of immune system in the growth of melanocytic nevi.

The time unit used in the simulation was year and the integration interval was set at *dt=0.04* years (in order to simulate the high mitotic activity during in utero period). The Euler's method of integration was used.

The process of mitosis was modeled as discrete time events in two compartments. In the first one the

mitoses during the *in utero* growth were modeled and in the second one mitoses from infancy to the age of 18 years (the approximately period which a person growth). The probability per cell per mitosis was set between to 10^{-9} and $4 \cdot 10^{-7}$ (in this model the mutation probability was hypothesized to be equal before and after birth).

To simulate the process of mitoses (as a discrete process) a container of the type Conveyor, with discrete time events, was used. Each discrete element (in this case melanocytes) after a discrete period of time exits the Conveyor and reenters in it duplicated (which represents mitosis). During the passage in the Conveyor the element could leak form it with a probability between 10^{-9} and $4 \cdot 10^{-7}$. The process represents the mutation probability during the process of mitosis (the leak zone was set also as a discrete time event). In the first Conveyor (Melanocytes 1) the passage time was 0.04 years while in the second one (Melanocytes 2) was 4.32 years. The results of the first part of the simulation model were similar with those obtained in the article that hypothesized the number of mutation needed to form a nevus. The number of melanocytes at the end of the process was approximately $2 \cdot 10^{9}$ in each performed simulation (the number of melanocytes in skin of an adult person). In Fig. 3 the results of the first part of the simulation a presented. Of all the possible parameters analyzed were selected only those which were capable to create at least 20 single nevomelanocytes (Nevus cells). The minimal probability of mutation per cell per mitosis needed to create at least 20 nevomelanocytes was 10^{-8} (Fig. 3B).

In the second part of the model three processes were simulated: 1. growth of nevi from single nevomelanocytes, 2. regression and disappearance of nevi and 3. disappearance of single nevomelanocytes.

We hypothesized that the process of disappearance of nevi and single melanocytes are equally modulated by the immune system, so the coefficient that determine their disappearance (probability of disappearance per time unit) (called f in the simulation) is in common (Fig. 2). The probability that the immune system let to a nevomelanocyte to develop into a clinically visible nevus is determined by the factor called in the model – Immune system (probability per time unit). The variable was independent form the parameter f (Fig. 2).

A series of simulation experiments with different values of the probability of mutation (greater that 10^{-8}), Immune system and f were conducted. The results were presented graphically and visually analyzed (Fig. 4 and 5).

From the picture can be seen that increasing the value of Immune system more single nevomelanocytes become nevi, while increasing the value of f less nevomelanocytes become nevi and existing nevi regress faster (Fig. 4A-E). Because of the great number of possible values that satisfies the minimal criteria no attempt to analyze all the data was done.

The last step in the analysis of the model was to simulate a short period of immunosuppression. Experimenting with the influence of the immune system, in the model, it can be created a "state of transient immunosuppression" with a consequent relatively fast appearance of nevi (Fig. 6). This part of the model is important because to form a great number of nevi a great number on single nevomelanocytes should exist. Taking into account this hypothetical information many of the values accepted as true (in the simulation model) can be rejected. In particular those were the number of nevomelanocytes is approximately less than 100.

Shortly, in all the theoretically acceptable simulations an approximately exponential increase in the number of nevi was visible before the second decade of life. The maximal number of nevi was present in the second and third decade of life with the regression (disappearance) of melanocytic nevi after that. Also, short period of immunosuppression can be simulated.

5 Discussion and conclusion

The main aim of the simulation model was not to obtain exact data form the model, but to make a rough analysis of the proposed theories on the number of mutations needed to form a nevus and the function of the immune system to control their proliferation.

Based on the results we concluded that the conceptual and simulation model support the theory on the number of mutations needed to form a nevus and that the immune system could be responsible in their growth and disappearance [5]. Using the model it was showed that there are more nevomelanocytes in the skin which do not develop into visible nevi because of some inhibitory effect (in our case the effect of immune system). The immune system in this case was divided in two parts: 1. control of the proliferation of nevomelanocytes and formation of visible nevus and 2. destruction of single nevomelanocytes and nevi. That was used because the mechanism of the possible immune influence on nevomelanocytes is not yet well defined, and there were no possibility to connect the two processes.

The model in some parts was simplified and did not take into account some problems that could be important in the formation of melanocytic nevi.

The possibility that the probability of mutation per cell per mitosis is different during the period *in utero* and in the different phases of the life is very probable, especially during the first two decade of life, because of the exposition to sunlight (UV radiations) while the mitotic activity of melanocytes is still present. That could be the reason for a higher mole count in patients who were exposed more to UV radiation during that period [11,12].

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Another simplification in the model is that the death of single nevomelanocytes (Nevus cells) has the same probability of the complete disappearance of a grown nevus. This could be not true because it is possible that different factors influence the nevus regression and death of single nevomelanocytes (i.e. a small number of cells in the nevus can survive and regenerate the nevus). The major assumption in this model is that the immune system has the major importance in the formation and regression of melanocytic nevi, but other factor not yet examined, could be at the basis of the process of regulation of nevi dynamics, while the immune system could merely a secondary process.

A second assumption that was made is that the effect of the immune system is constant during life, which can be true or not in the case of nevomelanocytes.

Despite that the conceptual and simulation model roughly but adequately simulate the processes in the dynamic of nevus formation and regression.

More detailed epidemiological and laboratory studies are needed to create a more detailed simulation model that would explain the formation of melanocytic nevi and the role of immune system in the proliferation of nevomelanocytes. Some of the most important data needed for a more exact model are: 1. the number of mutations needed to create a nevus, 2. more detailed studies on the size of melanocytic nevi at different age and prospective studies on the dynamic of nevi growth (and regression). Mathematical and simulation models in this case could be of great importance to test rough or more detailed theories on the development of nevi and above all melanoma.

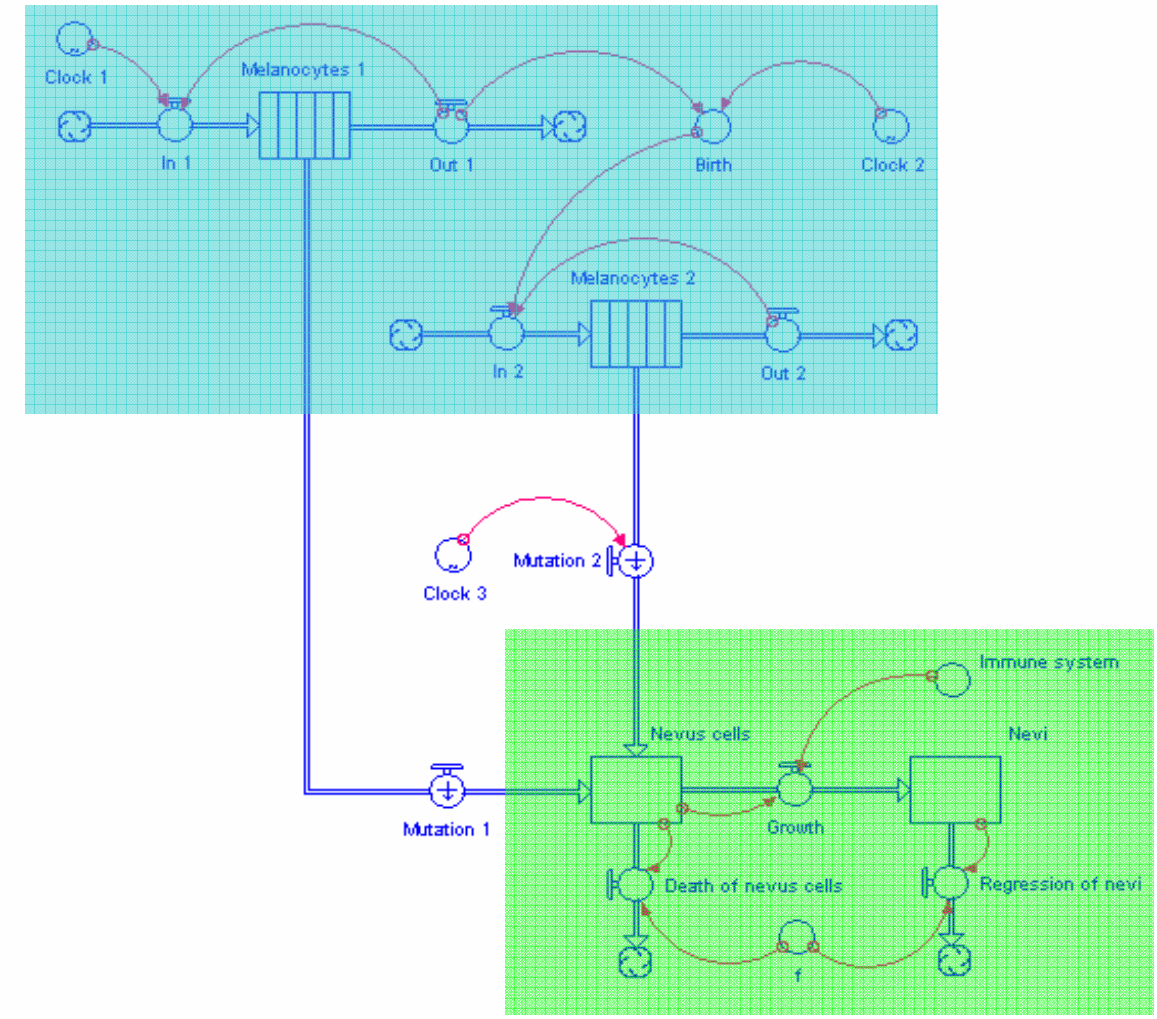

Fig. 2 The model has two main parts: the mitotic activity of melanocytes before and after birth (blue area) and the formation of nevi under the control of the immune system (green area)

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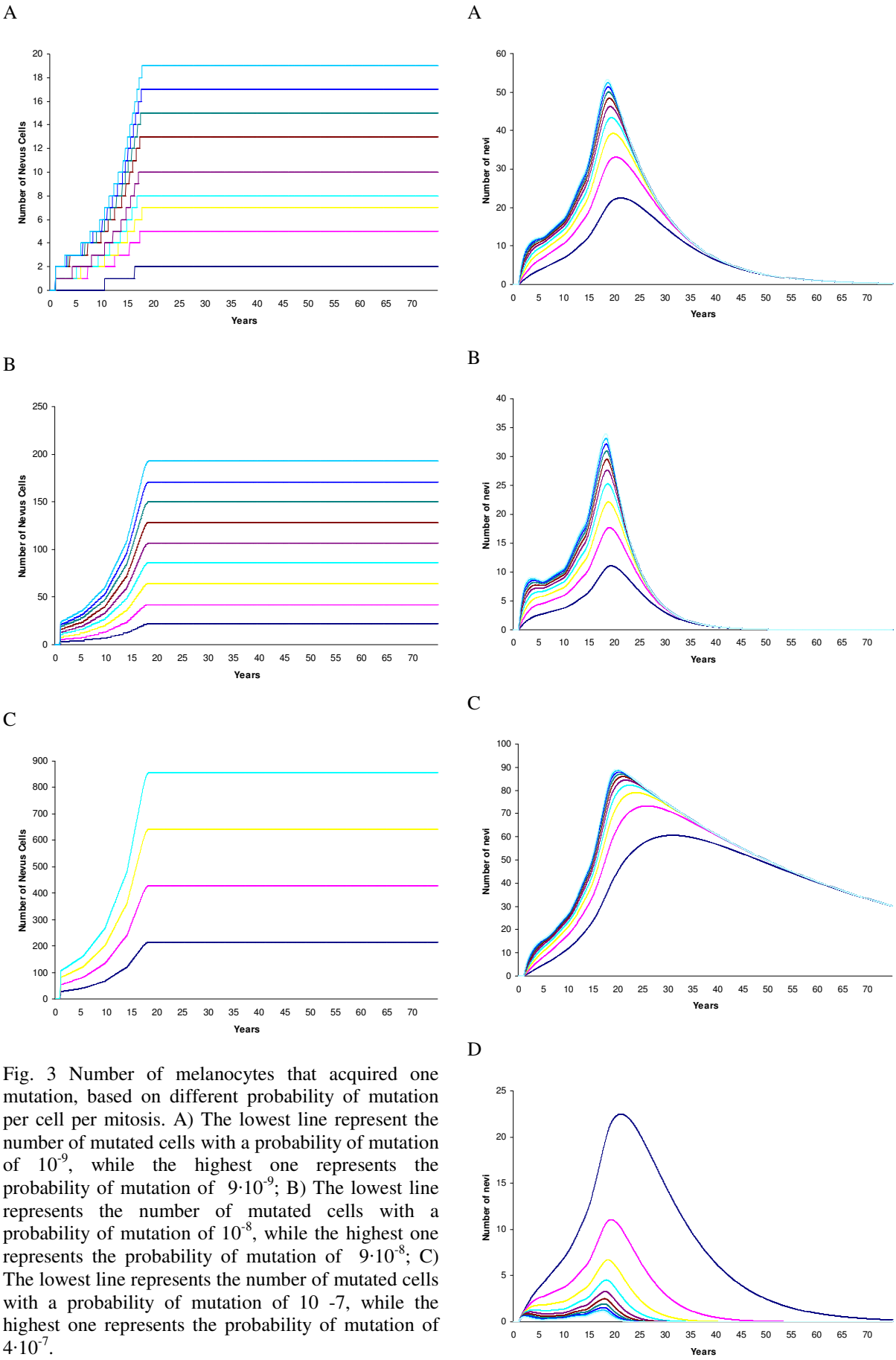

Fig. 3 Number of melanocytes that acquired one mutation, based on different probability of mutation per cell per mitosis. A) The lowest line represent the number of mutated cells with a probability of mutation of 10^{-9}, while the highest one represents the probability of mutation of $9 \cdot 10^{-9}$; B) The lowest line represents the number of mutated cells with a probability of mutation of 10^{-8}, while the highest one represents the probability of mutation of $9 \cdot 10^{-8}$; C) The lowest line represents the number of mutated cells with a probability of mutation of 10 -7, while the highest one represents the probability of mutation of $4 \cdot 10^{-7}$.

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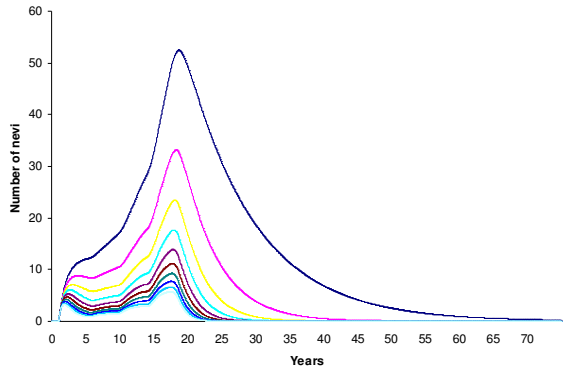

Fig. 4 Influence of Immune system and f on the number of nevi (probability of mutation in melanocytes was set at $5 \cdot 10^{-8}$). A) f=0.1, Immune system between 0.1 and 1 (step 0.1); B) f=0.2, Immune system between 0.1 and 1 (step 0.1); C) f=0.02, Immune system between 0.1 and 1 (step 0.1); D) Immune system 0.1, f between 0.1 and 1 (step 0.1); E) Immune system 0.9, f between 0.1 and 1 (step 0.1).

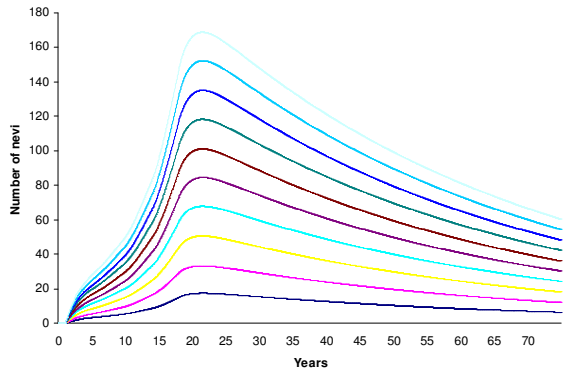

Fig. 5 The influence of the probability of mutation in melanocytes on the number of nevi (Immune system=0.5, f=0.02)

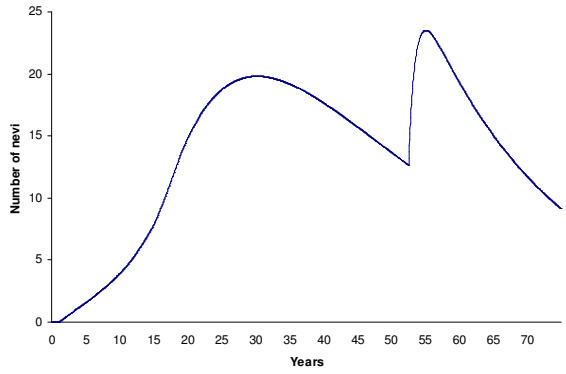

Fig. 6 A simulated immunosuppression that led to a fast increase in the number of nevi.

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