COMMENTARY

Mathematical Models for Human Cancer Incidence Rates - Application to Results from Europe, including North Cyprus

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Abstract

The overall cancer incidence rate declines at very old age. Possible causes of this decline include the effects of cross-sectional data that transform cohort dynamics into age patterns, population heterogeneity that selects individuals susceptible to cancer, a decline in some carcinogenic exposure in older individuals, underdiagnosis, and the effects of individual aging that slow down major physiological processes in an organism. Here several mathematical models contributing to the explanation of this phenomenon are discussed with extension of the Strehler and Mildvan model of aging and mortality to the analysis of data on cancer incidence at old age (data source: International Agency for Research on Cancer). The model can help explain the observed time trends and age patterns of cancer incidence rates.

Key Words: Cancer incidence - age dependence - mathematical models

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Introduction

The search for explanations of cancer rate patterns has a long history. Researchers studying the relationship between age and cancer mortality risk have focused on the increase in cancer mortality rates with age (Peto et al., 1975; Rainsford et al., 1985; Volpe and Dix, 1986; Dix 1989; Krtolica and Campisi 2002). They ignored other typical features of cancer rate patterns, such as deceleration and decline at old ages. A reason might be that they have used data on age-specific cancer mortality rather than incidence data. Data on cancer mortality are traditionally limited to age 75, which does not allow for observations on the decline in the rate at oldest ages (EUCAN and GLOBOCAN databases). Data from studies on age-specific cancer mortality among the oldest old, when combined with available data for earlier ages (Smith 1996, 1999], allow us to conclude that cancer mortality rates among the oldest old decline with age. In this paper, I will focus on possible explanations of typical patterns of the overall cancer incidence rates. Typical age-pattern features of the overall cancer incidence rate include (Figure 1):

(i) a peak during early childhood,
(ii) a low rate during youth,
(iii) an increase during adolescence,
(iv) deceleration or decline at old ages.

Decline in the cancer incidence rate is also observed in cohort data (Figure 2).

Age-specific incidence rates for different cancer sites have substantially different patterns due to different underlying mechanisms. For instance, hormonal instability at climacteric ages influences morbidity of diseases directly connected with the endocrine and immune balance

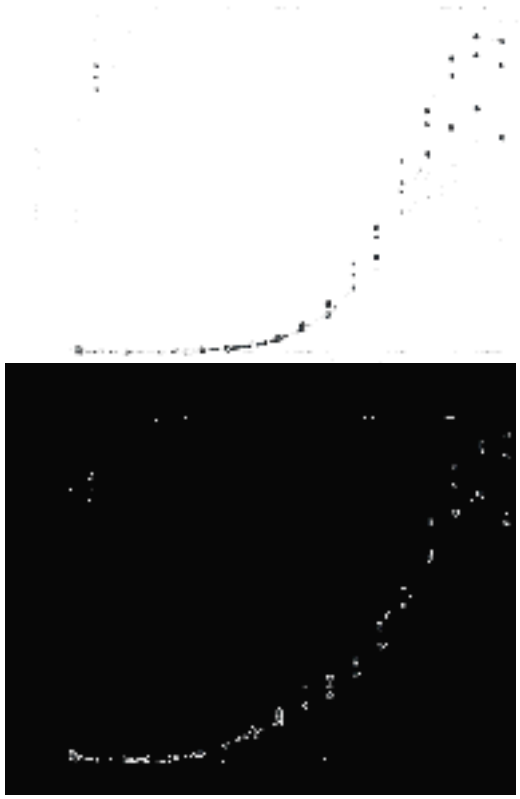

Figure 1 Female (A) and Male (B) cancer incidence rates in North Cyprus

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Figure 2. Female (thin lines) and Male (thick lines) Cohort Rates for Cancer Incidence. a) North Europe; b) South Europe

such as female hormone-dependent cancers (e.g., ovarian or endometrium cancers). This results in wave-like patterns of incidence rates for these sites. Nevertheless, some cancer sites have age-specific trajectories of incidence rates at old ages similar to the overall cancer incidence rates at these ages (i.e., a levelling-off or decline). This is observed for some of the most prevalent cancers such as lung, stomach and colon cancers for both males and females in different countries and time periods (Figure 3).

Site-specific analyses of cancer rates are very interesting and important. I think, however, that this should not exclude studies of the overall cancer incidence rates. This situation resembles the relationship between mortality by cause of death and total mortality in demography. Although studies of cause-specific mortality give us much more details concerning the mechanisms involved in mortality increase, the studies of total mortality are continuing partly because the shape of this curve exhibits remarkable regularity despite variability in trends in patterns of cause-specific mortality rates. For this reason I decided to focus on the overall cancer incidence rates and address questions related to cancers of specific sites in our further studies (Ukraintseva and Yashin, 2004).

Concerning the contribution of cancers of several sites into the decline of the overall cancer incidence rate, there is a common opinion that the shape of the incidence rate pattern is an invariant characteristic of a cancer site. For instance, it was proposed (on the base of data from the NC population of the past decade) that male lung cancer exhibits an exponential increase in the rate until the very old ages regardless of time and place differences. This implies that such a shape is an inherent trait of any lung

Figure 3. Age-specific Incidence Rates for Different Cancer Sites. a) North Cyprus (1990-2000); b) England (1990-2000); c) North Cyprus (2000-2004); d) Germany (1990-2004)

cancer pattern. Initially I believed that the specific traits of incidence rate patterns (e.g., manifestation of a peak rather than a levelling-off at old ages) mostly depend on a cancer site being its inherent feature as well. However, a detailed comparison of incidence rate curves showed the at their shape depends not only on cancer site and sex but also on time, place, and generally on prevalence of the respective cancer (IARC 1965-1997). For instance, male lung cancer was less prevalent in North Cyprus in the past and its age-pattern manifested a wave-like shape with a peak around ages 70-74 in the 1990s, while in the 2004s it exhibited a peak shifted to the older ages (Figure 3). In the UK, such a peak is absent nowadays but was exhibited in the past, in the 1930-1940s. Age-patterns of colon, breast, ovarian and stomach cancers also differ over time and place. These differences in the shape of incidence rate patterns for the same cancer site probably reflect time and place differences in carcinogenic exposures. The effects, being significant, may mask tissue-specific dependence of cancer risk on age. Despite such differences, the overall cancer rate patterns exhibit common features. This also justifies analyses of cancer incidence rates for all sites combined. Detection bias is a well recognized factor that plays an important role in defining age-related patterns of cancer incidence rates. The detection of new cases of cancer often involves complex diagnostic procedures. The use of a number of such procedures (e.g., colonoscopy) may be restricted in the oldest old ages, when individuals are frail, or have multiple chronic conditions. This may create the detection bias since a number of cancers may stay undetected among the oldest old. Forth is reason the deceleration or decline in the age pattern of cancer incidence rate at oldest old ages, calculated from the available data, may not necessarily reflect the real pattern of changes in cancer risk with age. Several studies have been performed to address this issue (Stanta et al. 1997) analyzed a group of 507 autopsies of elderly subjects, divided into three age groups, 75-90 years, 95-99, and over 99 (centenarians). The prevalence of cancer was 35% among the younger persons, and 20% and 16% respectively, for two other groups of the oldest old. Accuracy of diagnosis also declined in the oldest old. The authors concluded that both the incidence of cancer and the importance of cancer as a cause of death might decline after age 95 (Kuramoto et al. 1993). Cancer prevalence decreased with advancing age: 50.0% in the 1990-1992, 47.9% in the 1993-1996, 43.2% in the 1997-2000, and 39.3% in the 2001-2004. There is also evidence concerning cancer incidence turnover at old age in laboratory mice (Pompei et al. 2001).

These significant findings suggest that old age decline in cancer risk are not spurious. Indeed, for example, in the case of experimental animals, such decline can not be related to a diagnostic bias. Despite the fact that additional efforts are necessary to evaluate the contribution of detection bias into observed estimates of cancer incidence and mortality rates (Ukraintseva and Yashin, 2003), many cancer epidemiologists agree on a decelerating and even declining age pattern of these rates at oldest old ages. Few attempts have been made to explain the above developments in cancer rate curves. Some theories attribute the cancer risk patterns to diminished exposure to carcinogens (e.g., tobacco smoking) in older individuals (Peto et al., 1985), the effects of population heterogeneity (Vaupel and Yashin, 1988), and the paradoxical impact of physiological aging on cancer risks at old ages (Benson et al., 1996; Ukraintseva and Yashin, 2001). Below, I discuss different mathematical models that provide specific explanations for the cancer incidence rate patterns observed. I apply a modified Strehler and Mildvan model of aging to data on cancer incidence rates in different countries and different time periods (Strehler and Mildvan, 1960). I show that the model of carcinogenesis, which operates with some parameters of an organisms aging (with a possible extension to include heterogeneity), produces patterns of cancer incidence rates similar to those observed in human populations.

Data

I apply our model to data on human cancer incidence rates in different countries and different time periods. The NC data were compared with northern and southern European regions separately, in line with UN definitions [Statistical Year Book, State Planning Organization, Statistics and Research Department, 1999, 2001, 2002 and 2005]. Countries of South Europe (SE), including Mediterranean regions: Italy, France, Spain, Greece and Portugal. Countries of North Europe (NE): Austria, Germany, United Kingdom, Sweden, Denmark and Holland. In the text, "Europe" implies SE and NE countries combined. ASR data for SE and NE were obtained for the period 1990-2004 from EUROCIM of the European Network of Cancer Registries (ENCR) (EUROCIM Version 4.0.2001, Ferlay et al. 1988). The periods vary for different countries. The volumes each provide the female and male average annual cancer incidence per 100,000 over the corresponding time period for the specific country (province and/or ethnic group) in 5 -year age groups up to 85 and above (for some countries, the first group, 0-4, is separated into two groups: 0 and 1-4). The data are provided for separate sites and for all sites combined. The longest time series are available for North Cyprus. Each of the seven volumes contains data on the cancer incidence in this region. It therefore is the most appropriate data set to analyze changes in cancer incidence rates over time (Figure 1). Besides the North Cyprus data, I also look at cancer incidence rates in several European countries.

Models of Human Cancer Incidence Rates

Several types of models can explain the patterns and dynamics of human cancer incidence rates. In this section, I outline some of them and provide different explanations for the observed patterns of the rates. The application of these models to the available data is beyond the scope of this paper. Age-period-cohort models (APC models) are widely used to represent epidemiological data. They facilitate trend analysis in disease incidence and mortality over age, time, and birth cohort. Some additional efforts are needed to deal with identifiably problems (Robertson

et al., 1999). However, the main point here is that one is able to obtain the observed dynamics of the rates over age (an increase and then a levelling-off or decline) and an increase of the rates over time operating with the combinations of age, period and cohort effects. Another explanation of the decline in cancer incidence rates stems from differential selection in a heterogeneous population. Both discrete and continuous heterogeneity models provide possible explanations of this decline (Vaupel and Yashin, 1988). The mixture of two populations, one of which is prone to cancer and the other is not, results in a decline of the cancer incidence rate in the entire population due to the dying off of the susceptible sub-population (Vaupel and Yashin, 1985; 1988). A gamma-frailty model (Vaupel et al., 1979), with a Weibull baseline incidence shows a declining incidence rate at old ages at the population level. Age-period-cohort and heterogeneity models do not describe the internal biological processes that result in the observed rate dynamics. Other models that in corporate biological mechanisms of carcinogenesis also can explain the actual patterns of cancer incidence rates. The Armitage-Doll (AD) model (Armitage and Doll, 1954) uses a multistage theory of carcinogenesis to explain increases of cancer incidence rates with age. However, the AD model can not produce the decline in the rates. The Moolgavkar-Venzon-Knudson (MVK) model (Moolgavkar and Venzon, 1979; Moolgavkar and Knudson, 1981; Moolgavkar and Luebeck, 1990)) takes into account the dynamics of cell proliferation and differentiation in the process of carcinogenesis. The model, which has age-dependent intensities of proliferation and differentiation of normal and intermediate (pre-malignant) cells, results in age-related increases and declines of the rates. Yakovlev suggested a model of tumour development that operates with a set of cells (clonogens) capable of generating tumours in the long run (Yakovlev et al., 1993). The incidence rates are proportional to the probability distribution function of random variables representing the time for the clonogen to produce a detectable tumour (progression time). As a result, the incidence rates increase, level off, and decline with age. Individual aging models refer to age-associated changes in an organism that influence the chances of developing a disease. Ukraintseva and Yashin proposed a model of individual aging that operates with three components (basal, ontogenetic, and exposure-related) having different age-related dynamics in an organism (Ukraintseva and Yashin, 2001). The basic idea behind this model is that internal biological processes, which exhibit different age-related dynamics, are assumed to have a different influence on the age-specific probability of developing a disease. Any observed morbidity pattern in a population is the result of interaction between these processes (see details in section 4.2 below). The model can be incorporated into the Yakovlev and Tsodikov model of carcinogenesis to produce the observed patterns of human cancer incidence rates (Yakovlev and Tsodikov 1996). The role of individual age-related physiological changes that may change susceptibility to cancer with age can be captured by the Strehler and Mildvan (SM) model (Strehler and Mildvan, 1960). Below, I present a modification of the original SM model and apply the modified model to data on human cancer incidence rates in different regions and time periods.

Modifications of the Strehler and Mildvan Model

The original SM model has been widely applied to human total and cause- specific mortality data (Riggs and Millecchia, 1992; Riggs and Hobbs, 1998). An important feature of this model is the connection between age-related physiological declines in an organism and Gompertz mortality curves. The model can also be used to describe an increase in cancer incidence rates up to old ages. However, it can not produce the levelling off and decline observed in the rates at oldest ages. Some modifications of the model thus are necessary to reproduce the entire trajectory of cancer incidence rates. I start with the original SM model and then develop its modifications.

4.1 The original Strehler and Mildvan Model

Following Strehler and Mildvan [Strehler and Mildvan 1960], assume that an organism has a certain capacity to stay healthy (i.e., to have no tumors) at age x. This capacity or vitality is defined as a linear function of age:

$$V(x)=V_0(1-Bx) \qquad (1)$$

where parameter B characterizes the slope of the vitality curve. V_0 B in the Strehler and Mildvan model can be interpreted as the rate of physiological aging.

Suppose that the intensity of events associated with external stress (I designate it as $K(x)$) does not depend on age, i.e., $K(x) = K$. Let ε_D be an average magnitude of stress. Under these assumptions, the observed cancer incidence rates are

$$\mu(x) = Ke^{V(x)/\varepsilon D} = ae^{bx} \qquad (2)$$

where $a = Ke^{V0/\varepsilon 0}$, $b = \frac{V_0 B}{\varepsilon_D}$ there is the relationship between Gompertz parameters a and b ("Strehler-Mildvan correlation"):

$$\ln a = \ln K - b/B \qquad (3)$$

The straightforward application of the original Strehler and Mildvan model to human cancer incidence data [IARC 1990-2004] produces negative values of vitality $V(x)$ at oldest ages. To avoid these limitations, I suggest an extension of the SM model. Since the model includes a conception of the individual aging rate, I discuss available empirical data on the dynamics of internal biological processes in an organism. These dynamics can be used to define age patterns in the rate of individual aging.

4.2 Available Empirical Data on The Rate of Individual Aging

To analyze data from experimental biology on the dynamics of the individual aging rate, I first define this rate per se. To date, researchers have not reached a

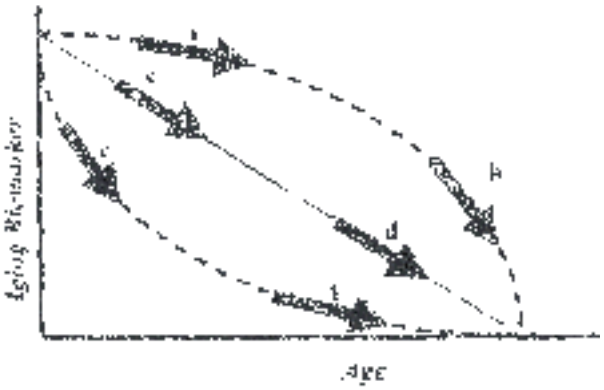

Figure 4. Three Representative Trajectories of Bio-markers of Aging (adapted from Nacamura et al., 1998)

consensus on the definition and ways of measuring an organisms aging rate. Several measures have been suggested, including the use of so named bio-markers of aging (Anstey et al., 1996; Dean, 1988; McClearn, 1997; Nakamura et al., 1998). A bio-marker of aging is an index of an organism's physiological state. The rate of individual aging can be measured as an increment (or decrement) in the value of the bio-marker per unit of age. It was shown that age-related changes in that bio-marker can be accelerated, decelerated, or be linear, depending on the variable chosen as the bio-marker (Figure 4).

We can see that a bio-marker of aging accelerates (ab), decelerates (ef), or assumes linearity (cd) with age in an organism. Correspondingly, the rate of aging, defined as the rate of change in the bio-marker, increases (in case of ab), decreases (in case of ef), or does not change (in case of cd) with age, depending on a variable chosen as the bio-marker of aging. This means that at the same time, and in the same organism, the rate of aging can be characterized by increasing, decreasing, or constant functions, depending on the index chosen as the bio-marker of aging.

Does this mean that all attempts to calculate individual aging rates as a universal index are useless? In some sense, yes. First, the rate of individual aging is not an obligatory constant during life. It may change in an individual with age (as shown by the curves 'ab' and 'ef' in Figure 4). Second, the aging phenotype results from age-related changes in an organism. These changes are often discordant (because the dynamics of separate age-related processes may be accelerated, decelerated, linear, or even wave-like). The relative contribution of these processes to the age phenotype may differ in individuals, creating significant variability in aging manifestations. For instance, some individuals look younger but are more vulnerable to disease than their peers, while others look older but are more resistant to acute stress, and as result live longer. What can I do, then, to study the rate of aging under such conditions? A solution is to subdivide individual aging into processes that show different age-related dynamics, and then to study these processes separately. Ukraintseva and Yashin (2001) applied this approach to explain patterns of age-specific morbidity in human populations. The authors divided all age-associated changes in an organism into three categories (basal, ontogenetic, and exposure-related) characterized by the decelerated, wave-like, and accelerated change in physiological in dices with age, respectively, and showed that these have a different (sometimes even opposite) influence on age-specific risks of common diseases, including cancer (Ukraintseva and Yashin, 2003).

Here I consider only basal changes in an organism. These are associated with the most frequently observed type of age-related dynamics of a bio-marker of aging: a decelerated change in the value of the bio-marker with age (as shown by curve 'ef' in Figure 4). The basal changes reflect the universal decline in the rates of basic biological processes during an organisms life such as the metabolism, cell proliferation and information processing rates. (Cheron and Desmedt, 1980; Grove and Kilgman, 1983; Dean, 1988; Remmen et al., 1995; Guyton and Hall, 1996; Rubin, 1997). Concerning basal changes, the main difference between an old and young individual is that the former lives, thinks, and does everything else slower than the young individual, that is, the rate of aging decreases in an organism with age. In consequence, many phenotypic effects of aging accumulate in an organism at a slower rate with age. For instance, an organism grows and gains weight at a slower rate (Figure 5a). The parameters of skin elasticity also change at a slower rate (Figure 5b) with age. The deceleration in the accumulation of phenotypic aging effects is noticeable even in age appearance: the percentage of gray haired individuals in a population increases at a slower rate with age (Keogh and Walsh, 1965) (Figure 5c).

4.3 Revised Strehler and Mildvan Model

Empirical data from studies of individual aging thus allow us to conclude that the rate of measured in accordance with the age-related dynamics of key physiological processes (such as metabolism and in formation processing) decreases with age, and changes in the respective bio-markers of aging decelerate with age in an individual. As to the SM model discussed above, this biological information allows us to make an

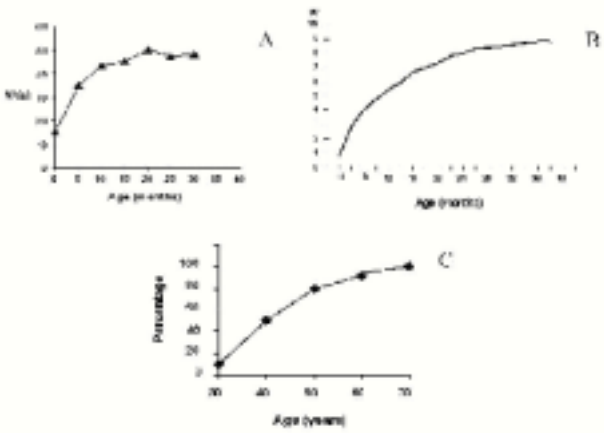

Figure 5. Examples of Change in a Biomarker of Aging at a Slower Rate with Age. A) Age-related change in the weight of ad libitum fed mice (Sohal and Weindruch 1996); B) Age-related change of tail collagen contraction in rats (Strehler 1962); (C) Hair graying among 3872 Australians (Keogh and Walsh 1965)

assumption about exponentially (instead of linearly) declined individual vitality with age. I assume that there is an age-related decline in the individual rate of change in this vitality. Hence, the vitality index is

$$V(x)=V_0e^{-Bx} \quad (4)$$

and the respective rate of individual aging, *r(x)*, can be defined as

$$r(x) = -dV(x)/dx = V_0Be^{-Bx} \quad (5)$$

Note that in the revised model, the rate of aging $r(x)=V_0Be^{-Bx}$ changes as the individual progresses in years, while it is constant during the individuals entire life in the original SM model, $r(x) = V_0B$

In the original SM model, parameter *B* characterizes the slope of the vitality curve. In the revised model, parameter *B* can be interpreted as the logarithmic rate of aging because

$$r_{\log}(x) = - -d(\log V(x)) /dx = dV(x)/dx \text{ x } 1/V(x)$$
$$= r(x)/ V(x) = B \quad (6)$$

In the revised model, parameter *B* characterizes the slope of the logarithmic vitality curve, log *V*(*x*), and the incidence rate is

$$\mu(x) = Ke^{\frac{V_0e^{-Bx}}{\varepsilon_D}} \quad (7)$$

or, defined through the individual rate of aging , *r*(*x*),

$$\mu(x) = Ke^{\frac{r(x)}{\varepsilon^B_D}} \quad (8)$$

4.4 Applying a Revised Strehler and Mildvan Model to Cancer Data

Epidemiological data show that changes in cancer incidence rates over time as well as differences in the rate among populations are closely associated with factors related to economic progress. In particular, the overall cancer incidence rate is commonly higher in the more developed countries. Usual explanations of this association involve improved diagnostics and increased exposure to environmental carcinogens (e.g., smoking and industrial pollution). Others concentrate on rising individual vulnerability to cancer and attribute improved medical and living conditions as well as better hygiene, among others factors, to this increase; these factors are seen to favour the relaxation of differential selection in a population and to increase the survival of frail individuals in a population. The revised SM model also explains the decrease in the overall cancer incidence rate at old ages (usually after 75) that is widely observed in epidemiological (both period and cohort) data. There are two different methods to obtain the declining rates.

First, I can obtain from this model the observed decline at oldest old ages and acceleration in the rates over time, assuming age-dependent parameter *K* (or, alternatively, parameter ε_D) and/or age-dependent parameter *B*. I formulate three modifications to the model (7):

a) Let the intensity of stress events be constant until some age *T* and after this age it starts to decline exponentially (as a manifestation of an older individual tending to avoid stresses):

$$K(xT) = \begin{cases} K & , x \le T \\ Ke^{-c_K(x-T)} & , x > T \end{cases} \quad (9)$$

where $0<C_K<<1$. Let $r(x)=B$ be constant. I will refer to model (7) with modification (9) as Model 1 throughout the text.

b) Assume that the intensity of stress events is constant at all ages but that the logarithmic rate of aging is changing over age. Assume, for instance, that this rate is constant until some age T and then it starts to decline exponentially [40]:

$$B(xT) = \begin{cases} B & , x \le T \\ Be^{-c_B(x-T)} & , x > T \end{cases} \quad (10)$$

where $0<C_B<<1$. I will refer to model (7) with modification (10) as Model 2 throughout the text.

c) Suppose that the intensity of stress events is modelled in the same way as in (a) but that at the same time the logarithmic rate of aging starts to increase exponentially:

$$K(xT) = \begin{cases} K & , x \le T \\ Ke^{-c_K(x-T)} & , x > T \end{cases} \quad (11)$$

$$B(xT) = \begin{cases} B & , x \le T \\ Be^{c_B(x-T)} & , x > T \end{cases} \quad (12)$$

where $0<C_K<<1$ and $0<C_B<<1$. . I will refer to model (7) with modification (11)-(12) as Model 3 throughout the text.

In all variants of the model, the resulting incidence rates decline at old ages.

Second, the observed dynamics of cancer incidence rates can also be obtained with the aging-independent parameters of the revised SM model, using a different approach. For this purpose, I include not only an exponentially decreasing rate of aging during life *r(x)* but also a factor of population heterogeneity, assuming variability in parameter *K*. The advantage of such an approach is that it allows us to consider both phenomena, a decrease in the individual rate of living with age and differential selection in a heterogeneous population within the framework of one model, explaining the decline in the overall cancer incidence rate at old ages.

To describe heterogeneity, suppose that each individual during his or her life has a specific value of intensity of stress events, denoted by *K*, and that this intensity is gamma distributed with mean 1 and variance. Assume that the other parameters of the revised SM model are deterministic. Then, the conditional incidence rate of such an individual is:

$$\mu(x|K) = Ke^{\frac{V_0e^{-Bx}}{\varepsilon_D}} \quad (13)$$

and, according to the well-known formula for the gamma-frailty model (Vaupel et al., 1979), the observed incidence rate in the population is:

$$\mu(x) = \mu_0(x)/(1+\sigma^2M_0(x)) \quad (14)$$

where $\mu_0(x) = e^{\frac{V_0 e^{-Bx}}{\varepsilon_D}}$ and $M_0(x) = \int_0^x \mu_0(t)dt$. I will refer to this model as Model 4 throughout the text.

Results

Models 1-4 were applied to data on human cancer incidence in different regions and time periods. The parameters were estimated using Maple's least-square routine. The estimations in all models for males and females are presented in Tables 1-8.

The four models provide an adequate fit to the data in different regions and time periods. Norms of differences and correlations between modelled and observed incidence rates for the same data set in Models 1-3 are comparable (see column s Norm and Corr in Tables 1-8). Model 3 has greater flexibility because it has an additional parameter and is capable of producing a better fit for some data sets. Model 4 fit least according to the norms of differences and correlations between modelled and observed incidence rates. Nevertheless, all four models capture the observed patterns of cancer incidence rates (except a peak in early childhood): a low rate in youth, an increase in this rate during adolescence, and a deceleration or decline at old ages. The models also produce non-declining rates when parameter T equals the maximal age of available data (85) or parameters C_B or C_K are zeros.

Estimations of parameters ε_D and *B* for the same data set are similar in Models 1-3 most cases. This is a predictable result because the models have, in essence,

Table 1. Revised SM Model with Changing Parameter *B* (Model 1) Applied to Female Cancer Incidence

Country	Period	K	10^{-5}	B	Norm	Corr
Germany	1990-1995	0.058	0.135	0.021	191.696	0.995
	1995-2000	0.110	0.132	0.016	352.533	0.988
	2000-2004	1.000	0.110	0.010	198.469	0.997
Denmark	1990-004	1.000	0.103	0.011	128.982	0.999
England	1990-1994	0.047	0.112	0.026	43.206	1.000
	1995-1999	0.057	0.111	0.025	72.608	1.000
	2000-2002	0.060	0.107	0.027	109.496	0.999
	2003-2004	0.025	0.123	0.029	51.960	1.000
Fınland	1990-2004	0.305	0.107	0.015	65.901	1.000
North	1990-1992	0.012	0.074	0.048	102.150	0.997
Cyprus	1993-1995	0.030	0.120	0.026	70.197	0.999
	1996-1998	0.089	0.112	0.018	29.176	1.000
	1999-2000	0.035	0.102	0.027	165.986	0.996
	2001-2002	0.363	0.110	0.012	63.448	0.999
	2002-2003	0.158	0.115	0.016	86.654	0.999
	2003-2004	0.497	0.110	0.012	97.018	0.999
Norway	1990-2004	0.103	0.124	0.017	53.642	1.000
Austria	1990-2004	0.028	0.118	0.028	49.262	1.000
Sweden	1990-2004	0.045	0.123	0.024	60.639	1.000
France	1990-2004	0.164	0.124	0.016	100.404	0.999
South	1990-1993	0.023	0.085	0.044	94.760	0.999
Europe	1994-1996	0.022	0.065	0.052	127.088	0.999
	1997-1999	0.036	0.089	0.038	107.922	0.999
	2000-2002	0.033	0.070	0.044	105.602	1.000
	2003-2004	0.047	0.084	0.036	74.000	1.000
North	1990-1993	0.078	0.123	0.020	65.764	1.000
Europe	1994-1996	0.051	0.119	0.024	60.194	1.000
	1997-1999	0.063	0.126	0.023	17.026	0.998
	2000-2002	0.036	0.095	0.034	46.124	1.000
	2003-2004	0.062	0.102	0.028	42.899	1.000

Norm, norm of differences; Corr, correlation between modelled and observed incidence rates

Table 2. Revised SM Model with Changing Parameter *B* (Model 1) Applied to Male Cancer Incidence

Country	Period	K	10^{-5}	B	Norm	Corr
Germany	1990-1995	0.137	0.077	0.025	85..393	1.000
	1995-2000	1.000	0.083	0.015	175.655	0.999
	2000-2004	0.140	0.069	0.029	116.747	1.000
Denmark	1990-004	0.109	0.071	0.028	73.549	1.000
England	1990-1994	0.093	0.047	0.038	80.396	1.000
	1995-1999	0.097	0.044	0.039	90.614	1.000
	2000-2002	0.409	0.063	0.025	91.954	1.000
	2003-2004	0.040	0.042	0.047	95.988	1.000
Fınland	1990-2004	0.046	0.039	0.048	92.821	1.000
North	1990-1992	0.037	0.047	0.044	179.777	0.997
Cyprus	1993-1995	0.113	0.074	0.027	125.413	0.999
	1996-1998	0.063	0.050	0.037	132.290	0.999
	1999-2000	0.107	0.059	0.031	77.651	1.000
	2001-2002	0.047	0.043	0.044	139.066	0.999
	2002-2003	0.070	0.051	0.039	67.173	1.000
	2003-2004	0.061	0.044	0.043	92.723	1.000
Norway	1990-2004	0.158	0.061	0.027	85.852	1.000
Austria	1990-2004	0.022	0.020	0.066	100.662	0.999
Sweden	1990-2004	0.059	0.047	0.039	95.218	1.000
France	1990-2004	0.071	0.048	0.041	122.441	1.000
South	1990-1993	0.088	0.047	0.039	120.991	1.000
Europe	1994-1996	0.105	0.048	0.038	135.613	1.000
	1997-1999	0.247	0.065	0.027	85.481	1.000
	2000-2002	0.301	0.076	0.024	201.148	1.000
	2003-2004	0.150	0.063	0.032	418.375	0.998
North	1990-1993	0.071	0.059	0.036	75.361	1.000
Europe	1994-1996	0.092	0.054	0.035	75.385	1.000
	1997-1999	0.361	0.069	0.024	183.061	0.999
	2000-2002	0.118	0.053	0.035	100.591	1.000
	2003-2004	0.289	0.066	0.026	72.377	1.000

Norm, norm of differences; Corr, correlation between modelled and observed incidence rates

Table 3. Revised SM Model with Changing Parameter *K* (Model 1) Applied to Female Cancer Incidence

Country	Period	K	10^{-5}	B	Norm	Corr
Germany	1990-1995	0.058	0.135	0.021	152.586	0.997
	1995-2000	0.110	0.132	0.016	352.533	0.988
	2000-2004	1.000	0.110	0.010	198.469	0.997
Denmark	1990-004	1.000	0.103	0.011	128.982	0.999
England	1990-1994	0.047	0.112	0.026	43.206	1.000
	1995-1999	0.057	0.111	0.025	72.608	1.000
	2000-2002	0.060	0.107	0.027	109.742	0.999
	2003-2004	0.025	0.123	0.029	51.960	1.000
Fınland	1990-2004	0.305	0.107	0.015	65.901	1.000
North	1990-1992	0.012	0.074	0.048	102.150	0.997
Cyprus	1993-1995	0.030	0.120	0.026	70.197	0.999
	1996-1998	0.089	0.112	0.018	29.177	1.000
	1999-2000	0.035	0.102	0.027	165.986	0.996
	2001-2002	0.363	0.110	0.012	63.448	0.999
	2002-2003	0.158	0.115	0.016	86.654	0.999
	2003-2004	0.497	0.110	0.012	97.018	0.999
Norway	1990-2004	0.103	0.124	0.017	53.642	1.000
Austria	1990-2004	0.028	0.118	0.028	49.262	1.000
Sweden	1990-2004	0.045	0.123	0.024	60.639	1.000
France	1990-2004	0.164	0.124	0.016	100.404	0.999
South	1990-1993	0.023	0.085	0.044	94.760	0.999
Europe	1994-1996	0.022	0.065	0.052	127.946	0.999
	1997-1999	0.036	0.089	0.038	118.832	0.999
	2000-2002	0.033	0.070	0.044	113.724	1.000
	2003-2004	0.047	0.084	0.036	74.000	1.000
North	1990-1993	0.078	0.123	0.020	65.764	1.000
Europe	1994-1996	0.051	0.119	0.024	60.194	1.000
	1997-1999	0.063	0.126	0.023	173.026	0.998
	2000-2002	0.036	0.095	0.034	46.124	1.000
	2003-2004	0.062	0.102	0.028	46.894	1.000

Norm, norm of differences; Corr, correlation between modelled and observed incidence rates

Table 4. Revised SM Model with Changing Parameter *B* (Model 1) Applied to Male Cancer Incidence

Country	Period	K	10^{-5}	B	Norm	Corr
Germany	1990-1995	0.125	0.076	0.026	81.041	1.000
	1995-2000	1.000	0.083	0.015	175.655	0.999
	2000-2004	0.621	0.078	0.019	82.233	1.000
Denmark	1990-004	0.109	0.071	0.028	73.549	1.000
England	1990-1994	0.093	0.047	0.038	80.396	1.000
	1995-1999	0.097	0.044	0.039	90.614	1.000
	2000-2002	0.552	0.065	0.023	100.755	1.000
	2003-2004	0.040	0.042	0.047	90.716	1.000
Fınland	1990-2004	0.046	0.039	0.048	97.569	1.000
North	1990-1992	0.037	0.047	0.044	185.281	0.997
Cyprus	1993-1995	0.103	0.073	0.028	126.693	0.999
	1996-1998	0.636	0.073	0.019	92.801	1.000
	1999-2000	0.107	0.059	0.031	77.651	1.000
	2001-2002	0.047	0.043	0.044	139.066	0.999
	2002-2003	0.070	0.051	0.039	67.173	1.000
	2003-2004	0.061	0.044	0.043	92.723	1.000
Norway	1990-2004	0.138	0.059	0.028	81.403	1.000
Austria	1990-2004	0.022	0.020	0.066	100.662	0.999
Sweden	1990-2004	0.059	0.047	0.039	95.218	1.000
France	1990-2004	0.071	0.048	0.041	122.441	1.000
South	1990-1993	0.088	0.047	0.039	120.991	1.000
Europe	1994-1996	0.105	0.048	0.038	135.613	1.000
	1997-1999	0.251	0.065	0.027	84.515	1.000
	2000-2002	0.301	0.076	0.024	201.148	1.000
	2003-2004	0.149	0.063	0.032	418.375	0.998
North	1990-1993	0.104	0.067	0.030	74.717	1.000
Europe	1994-1996	0.092	0.054	0.035	75.385	1.000
	1997-1999	0.068	0.037	0.046	257.278	0.999
	2000-2002	0.118	0.053	0.035	100.591	1.000
	2003-2004	0.289	0.066	0.026	72.377	1.000

Norm, norm of differences; Corr, correlation between modelled and observed incidence rates

Table 5. Revised SM Model with Changing Parameters *B* and *K* (Model 2) Applied to Female Cancer Incidence

Country	Period	K	10^{-5}	B	Norm	Corr
Germany	1990-1995	0.058	0.135	0.021	152.586	0.997
	1995-2000	0.018	0.082	0.042	167.098	0.997
	2000-2004	0.122	0.133	0.016	155.432	0.998
Denmark	1990-004	0.117	0.123	0.018	66.652	1.000
England	1990-1994	0.034	0.102	0.032	26.622	1.000
	1995-1999	0.043	0.102	0.029	40.340	1.000
	2000-2002	0.041	0.092	0.033	57.376	1.000
	2003-2004	0.018	0.109	0.035	42.603	1.000
Fınland	1990-2004	0.307	0.107	0.015	65.901	1.000
North	1990-1992	0.012	0.074	0.048	102.150	0.997
Cyprus	1993-1995	0.030	0.120	0.026	70.197	0.999
	1996-1998	0.089	0.112	0.018	29.177	1.000
	1999-2000	0.035	0.102	0.027	165.986	0.996
	2001-2002	0.359	0.110	0.013	63.448	0.999
	2002-2003	0.157	0.115	0.016	86.654	0.999
	2003-2004	0.492	0.110	0.012	97.018	1.000
Norway	1990-2004	0.085	0.125	0.018	52.801	1.000
Austria	1990-2004	0.031	0.120	0.027	48.530	1.000
Sweden	1990-2004	0.045	0.123	0.024	60.639	1.000
France	1990-2004	0.090	0.125	0.020	88.062	0.999
South	1990-1993	0.023	0.085	0.044	94.760	0.999
Europe	1994-1996	0.020	0.055	0.056	121.883	0.999
	1997-1999	0.034	0.087	0.039	118.832	1.000
	2000-2002	0.038	0.080	0.040	104.415	1.000
	2003-2004	0.053	0.089	0.033	70.029	1.000
North	1990-1993	0.043	0.118	0.026	56.034	1.000
Europe	1994-1996	0.051	0.119	0.024	60.194	1.000
	1997-1999	0.026	0.089	0.040	49.378	1.000
	2000-2002	0.033	0.091	0.036	43.516	1.000
	2003-2004	0.062	0.102	0.028	46.894	1.000

Norm, norm of differences; Corr, correlation between modelled and observed incidence rates

Table 6. Revised SM Model with Changing Parameters *K* and *B* (Model 2) Applied to Male Cancer Incidence

Country	Period	K	10^{-5}	B	Norm	Corr
Germany	1990-1995	0.133	0.077	0.025	73.954	1.000
	1995-2000	0.042	0.059	0.039	134.202	0.999
	2000-2004	0.769	0.079	0.018	74.564	1.000
Denmark	1990-004	0.077	0.063	0.032	63.769	1.000
England	1990-1994	0.170	0.059	0.030	62.464	1.000
	1995-1999	0.138	0.052	0.033	86.959	1.000
	2000-2002	0.525	0.066	0.023	100.755	1.000
	2003-2004	0.040	0.042	0.047	90.169	1.000
Fınland	1990-2004	0.046	0.039	0.048	97.569	1.000
North	1990-1992	0.037	0.047	0.044	185.281	0.997
Cyprus	1993-1995	0.103	0.073	0.028	126.693	0.999
	1996-1998	1.000	0.073	0.017	66.644	1.000
	1999-2000	0.107	0.059	0.031	77.651	1.000
	2001-2002	1.000	0.079	0.016	87.701	1.000
	2002-2003	0.110	0.062	0.032	44.426	1.000
	2003-2004	0.075	0.051	0.039	86.862	1.000
Norway	1990-2004	0.167	0.062	0.026	77.042	1.000
Austria	1990-2004	0.024	0.024	0.061	98.582	0.999
Sweden	1990-2004	0.059	0.046	0.039	95.218	1.000
France	1990-2004	0.071	0.048	0.041	122.441	1.000
South	1990-1993	0.154	0.061	0.031	116.389	1.000
Europe	1994-1996	0.323	0.066	0.025	95.222	1.000
	1997-1999	0.251	0.065	0.027	84.515	1.000
	2000-2002	1.000	0.079	0.018	172.146	1.000
	2003-2004	1.000	0.078	0.019	318.194	0.999
North	1990-1993	0.108	0.068	0.030	65.152	1.000
Europe	1994-1996	0.107	0.057	0.033	73.660	1.000
	1997-1999	1.000	0.075	0.018	203.271	0.999
	2000-2002	0.286	0.068	0.025	93.045	1.000
	2003-2004	0.395	0.068	0.024	69.551	1.000

Norm, norm of differences; Corr, correlation between modelled and observed incidence rates

Table 7. Revised SM Model with Heterogeneity in Parameter *K* (Model 1) Applied to Female Cancer Incidence

Country	Period	σ^2	10^{-5}	B	Norm	Corr
Germany	1990-1995	4.871	0.087	0.016	371.808	0.981
	1995-2000	0.359	0.111	0.010	360.808	0.987
	2000-2004	1.769	0.099	0.013	396.752	0.987
Denmark	1990-2004	0.816	0.098	0.013	259.680	0.996
England	1990-1994	1.330	0.100	0.012	80.357	1.000
	1995-1999	1.121	0.100	0.012	101.505	0.999
	2000-2002	1.077	0.099	0.013	139.143	0.999
	2003-2004	2.332	0.103	0.011	82.781	0.999
Fınland	1990-2004	1.786	0.089	0.014	113.617	0.999
North	1990-1992	9.903	0.072	0.019	264.653	0.999
Cyprus	1993-1995	8.503	0.074	0.018	304.107	0.981
	1996-1998	4.122	0.083	0.014	129.228	0.977
	1999-2000	3.504	0.084	0.014	154.502	0.997
	2001-2002	4.799	0.081	0.015	190.424	0.996
	2002-2003	3.248	0.086	0.014	153.448	0.994
	2003-2004	2.622	0.092	0.013	166.928	0.997
Norway	1990-2004	1.051	0.102	0.011	61.494	0.997
Austria	1990-2004	5.252	0.086	0.015	145.189	1.000
Sweden	1990-2004	4.112	0.087	0.015	194.733	0.996
France	1990-2004	0.494	0.107	0.011	111.439	0.995
South	1990-1993	2.534	0.098	0.015	137.054	0.999
Europe	1994-1996	2.689	0.094	0.016	153.555	0.999
	1997-1999	2.191	0.093	0.016	130.010	0.999
	2000-2002	2.433	0.084	0.018	97.051	0.999
	2003-2004	2.757	0.076	0.019	218.568	1.000
North	1990-1993	1.654	0.098	0.013	117.910	0.998
Europe	1994-1996	1.988	0.097	0.013	82.540	0.999
	1997-1999	0.840	0.108	0.011	207.190	0.999
	2000-2002	1.803	0.095	0.014	68.730	1.000
	2003-2004	2.654	0.084	0.017	101.588	0.999

Norm, norm of differences; Corr, correlation between modelled and observed incidence rates

Table 8. Revised SM Model with Heterogeneity in Parameter *K* (Model 1) Applied to Male Cancer Incidence

Country	Period	σ^2	10^{-5}	B	Norm	Corr
Germany	1990-1995	2.683	0.061	0.021	110.189	1.000
	1995-2000	1.624	0.066	0.020	337.911	0.996
	2000-2004	1.283	0.063	0.021	130.952	1.000
Denmark	1990-004	1.641	0.064	0.020	204.059	0.998
England	1990-1994	1.401	0.055	0.024	113.275	1.000
	1995-1999	1.107	0.057	0.023	83.649	1.000
	2000-2002	0.703	0.062	0.022	149.752	1.000
	2003-2004	2.219	0.066	0.020	80.981	1.000
Fınland	1990-2004	2.397	0.058	0.024	80.926	1.000
North	1990-1992	5.552	0.045	0.027	219.281	0.996
Cyprus	1993-1995	6.596	0.033	0.033	398.346	0.987
	1996-1998	4.108	0.040	0.028	273.474	0.996
	1999-2000	2.912	0.042	0.027	388.519	0.995
	2001-2002	3.285	0.047	0.026	252.474	0.997
	2002-2003	2.174	0.053	0.024	194.626	0.999
	2003-2004	1.948	0.055	0.024	166.106	0.999
Norway	1990-2004	2.170	0.058	0.021	73.705	1.000
Austria	1990-2004	6.482	0.036	0.031	281.685	0.993
Sweden	1990-2004	3.324	0.045	0.026	227.656	0.998
France	1990-2004	1.174	0.065	0.021	138.767	1.000
South	1990-1993	1.673	0.050	0.026	239.428	0.999
Europe	1994-1996	1.493	0.050	0.026	184.484	1.000
	1997-1999	1.024	0.060	0.023	102.437	1.000
	2000-2002	1.082	0.058	0.024	289.353	0.999
	2003-2004	1.462	0.046	0.028	492.903	0.998
North	1990-1993	1.541	0.066	0.020	66.905	1.000
Europe	1994-1996	2.041	0.051	0.025	226.711	0.999
	1997-1999	0.866	0.067	0.021	277.710	0.999
	2000-2002	1.187	0.056	0.024	175.271	1.000
	2003-2004	1.571	0.044	0.028	399.447	0.998

Norm, norm of differences; Corr, correlation between modelled and observed incidence rates

the same incidence rate until age *T* and then differ either in the slope of the vitality function or the intensity of stress events in age interval [*T*, 85]. The estimations, however, show variability between different data sets, reflecting substantial variability between the observed rates in different countries and changes in the rates over time in the same country. For instance, the North Cyprus prefecture incidence rates at oldest old ages almost doubled from 1990-2004 (Figure 1). Parameters *K*, and *B* define the patterns of incidence rates and, therefore, are also subject to variability over time and place. The models are less sensitive to changes in parameter K and, in some cases, this parameter varies to a greater extent in Models 1-3 and in different data sets with in the same model. I restricted the parameter *K* to be less than 10^5 in our models. In some cases, the estimations of *K* reach the upper boundary, but the greater values of *K* would result only in a minor improvement of fit. I also assumed *T* to be greater than 70 (around the minimal age of decline in the incidence rates) and the estimations are at boundary in some cases. However, a further reduction of the lower boundary gives no substantial improvement of fit.

Model 4 also captures the observed pattern of cancer incidence rates, except for peak in early childhood. Parameters ε_D and *B* have the same meaning and the same effect on the shape of the incidence rate as their counterparts in Models 1-3, and their estimations lie within the range of the estimations in Models 1-3. Estimations of (variance of the heterogeneity variable) lie within the range 0.36-9.91. This reflects a possible variability in the susceptibility to stress in different populations at different times. Larger variances may be related to a more pronounced decline of the rate in the mid-1995.

The models with a constant logarithmic rate of aging B over age (Model 1), a decreasing *B* at oldest ages (Model 2) and an increasing *B* at oldest ages (Model 3) result in declining patterns of cancer incidence rates. This means that the observed decline in the rates may be the result of three different dynamics of the logarithmic rates of aging and intensities of stress events related to cancer. I interpret these changes as a more pronounced manifestation of the basal component of aging within the context of Ukraintseva and Yashin's model (2001). The logarithmic rate of aging possibly does not change with age, in contrast to the intensity. I can also assume that the intensity is fixed over age, whereas the logarithmic rate of aging declines at oldest old ages. As a variation of the first model, I can assume that the declining intensity at advanced ages is accompanied by an increasing logarithmic rate of aging. Note that I rather can alternatively impose changes on the average amplitude of stress events ε_D than intensity *K*.

Male and female cancer incidence rates are different. Males have higher incidence rates at older ages than the opposite sex. The stable relationship between the estimations for male and female data in Model 4 reflects this observation. The resulting estimates of are higher for females in all data set, while the estimates of B are always higher for males (see Tables 7-8). A trade-off between resource allocation strategies in the male and female organisms, i.e., between average amplitudes of stress events and the rates of physiological aging, possibly explains this phenomenon. The female organism spends a greater part of her resources on 'protection' against physiological aging. As a result, the values of *B* are lower and that of ε_D are higher. The male organism, on the contrary, fights harmful influences and therefore reduces the amplitude of stress events that reach the organism. Thus, corresponding parameters ε_D are lower than that of females, but the trade-off is the higher rate of physiological aging *B*.

The observed increase in cancer incidence rates over time can be obtained in the Models 1-4 if, for instance, one of the parameters ε_D and *B* is increasing over time and second is constant or declining. Then, changes in parameters ε_D and *B* can also be interpreted in terms of changes in resource allocation strategies over time.

Conclusion

The literature on mathematical models of carcinogenesis is vast (Yakovlev and Tsodikov 1996; Moolgavkar et al., 1999; van Leeuwen and Zonneveld 2001). In this paper, I mentioned several very specific mathematical models only, and they had been selected to explain observed trends in overall cancer incidence rates. I also analyzed data on cancer incidence rates in different region s at different periods, applying the revised SM model (both with age-dependent parameters and with heterogeneity). These models suggest different reasons

for the observed patterns of overall cancer incidence rates. The analyses of the models demonstrate that:

1) The observed decline in overall human cancer incidence rates at old ages can be a pronounced manifestation of the basal component of individual aging. This result can be obtained by a decline (over age) in the related parameter of the logarithmic rate of aging (parameter *B* in Model 2) or by an age-related decline in intensity of external stresses at old ages (parameter *K* in Model 1).

2) Effects of population heterogeneity in the susceptibility to external stresses can also explain this decline (Model 4). In this model, differences in values of variance of the heterogeneity distribution explain differences in the rates of decline at old ages observed in different populations and time periods.

3) The models are capable of explaining the interesting phenomenon observed in the overall cancer incidence rates, namely the intersection of male/female rates. This universal pattern may be a result of different resource allocation strategies (fighting external stresses and fighting physiological aging) that are used by the male and female organisms. This intriguing pattern needs further explanation, from both a biological and a mathematical perspective. Available molecular-biological and epidemiological data allow for the development of more sophisticated mathematical models of these mechanisms.

4) The observed increase in cancer incidence rates over time can be interpreted in terms of changes in the resource allocation strategies over time (i.e., resource allocation between 'fighting' external stresses and 'fighting' physiological aging). Over-time trends in parameters of Models 1-4 (when one of the parameters ε_D or *B* and the second is constant or declining over time) can reflect this phenomenon.

The results also stimulate development of more detailed models and accumulation of more data on dynamics of physiological indices with age. Further analyses are necessary to gain a deeper understanding of the impact of age-related physiological changes on morbidity. Available data do not allow evaluating age-related changes in internal parameters that lead to increased chances of developing a disease with age. Extensive epidemiological and molecular-biological studies are needed to obtain time-series data on changes in stress-resistance with age (e.g., cellular sensitivity to oxidative stress). This permits associations to be made between the unspecified physiological index ('vitality') and real physiological parameters. Applications of various models that incorporate the observed physiological parameters to large time series data on human morbidity and mortality can help to obtain deeper insights into the possible mechanisms that regulate aging-related changes in the physiological parameters elucidate various factors responsible for the modification of the respective patterns over time and target appropriate prophylaxis to reduce physiological decline. In this paper, I focused mainly on biological explanations of observed declines in the age-trajectories of human cancer incidence rates. This does not mean that other explanations should not be taken into account. The dynamics of age-specific cancer incidence rates over time reflects the combined influence of various factors (social, behavioural, environmental, medical etc). The possible causes of this decline include:

(i) The effects of cross-sectional data that transform cohort dynamics in to age patterns,

(ii) Population heterogeneity that selects individuals susceptible to cancer,

(iii) A decline in some carcinogenic exposures in older individuals,

(iv) Underdiagnostics in older people it leads to a smaller detection number of new cases existing latently, and

(v) The effects of individual aging that slow down major physiological processes in an organism.

None of these factors can be neglected. The first four causes have been discussed in the literature to some extent.

In conclusion, the present paper provided some new insights into possible biological explanations for the observed phenomena. More elaborated models are needed to incorporate all of them and reveal the relative impact of these factors on observed trends. This would provide the grounds for fruitful discussions and stimulate further research directions. Changes in social, behavioural, environmental, and medical conditions would induce changes in internal (molecular-biological) mechanisms that are responsible for cancer development. If a convincing rationale is available for representing a disease etiology in a specific mathematical model, it should not to be ignored in data analysis.

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