Difference between Male and Female Cancer Incidence Rates: How Can It Be Explained?

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Summary. Age patterns of male and female cancer incidence rate do not look similar. This is because of the biologically based difference in susceptibility to cancer of different sites. This argument, however, does not clarify how age patterns of male and female cancer incidence rate must look like. The analysis of epidemiological data on cancer in different countries and in different years shows that male and female cancer incidence rates intersect around the age of female climacteric. We explain the observed pattern using the difference in ontogenetic components of aging between males and females. The explanation requires a new model of carcinogenesis, which takes this difference into account. Application to data on cancer incidence in Japan (Miyagi prefecture) illustrates the model.

Key words: cancer , model, incidence , ontogenesis

1 Introduction

The analysis of epidemiological data on cancer in different countries and at different time periods reveals common age patterns and universal time-trends in cancer incidence rates. Some of these features have been observed and discussed before. These include an increase of cancer incidence rate over time, both for males and females, and an increase, a leveling-off, and then a decline of the age pattern of this rate. Note that a consensus among cancer epidemiologists has not been arrived at concerning the explanation of these phenomena.

The new interesting feature is related to the joint pattern of cancer incidence rate for males and females. The data show strange regularity in relative

behavior of male and female cancer incidence rates. In all countries and time periods, these curves intersect at the interval of ages near female climacteric. For all investigated countries at different time periods, the total cancer incidence rates for females are higher than those for males up to middle age (near the age of female climacteric). After that the incidence rates for females become lower than for males. The growth of incidence rates over age is much more rapid for males than for females. In the latter case the growth is nearly linear (Fig. 1). Similar effects are also observed in cohort data (Fig. 2).

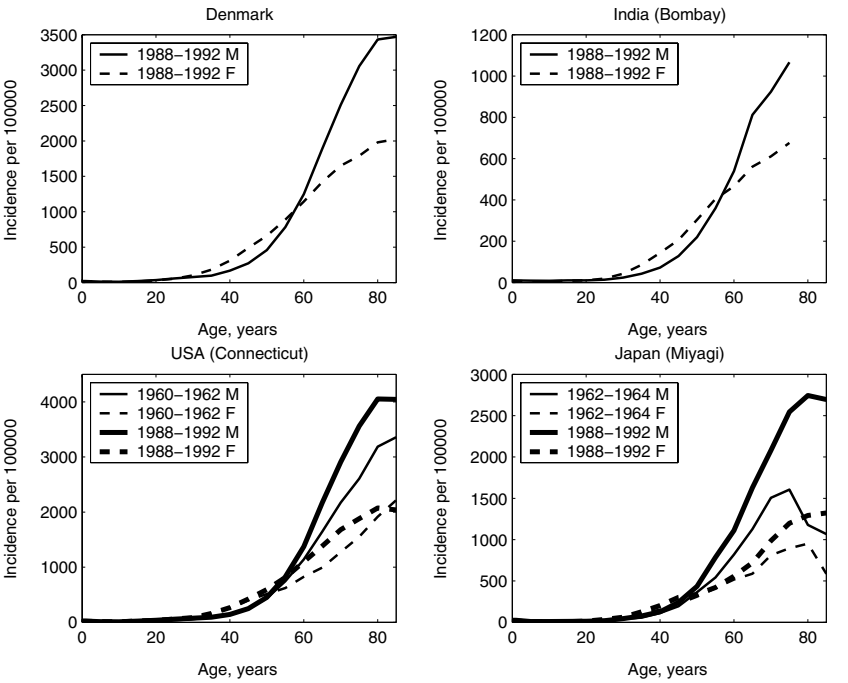

Fig. 1. Typical patterns of intersection between male and female overall cancer incidence rates: Denmark (1988–1992), India (Bombay, 1988–1992), USA (Connecticut, 1960–1962 and 1988–1992), and Japan (Miyagi prefecture, 1962–1964 and 1988–1992). 'M' – males, 'F' – females; data source: [3]–[9].

Common sense suggests that male and female age patterns of overall cancer incidence rate must differ because of biologically-based differences in specific cancer sites (such as breast, ovarian cancers for females and prostate cancer for males). However, the differing age-pattern, and its relative stability over time and place, cannot be predicted from such a consideration.

The differences in mechanisms involved in cancer initiation and development for males and females would be better understood if one could explain forces shaping the age-trajectories of cancer incidence rates, evaluate the role

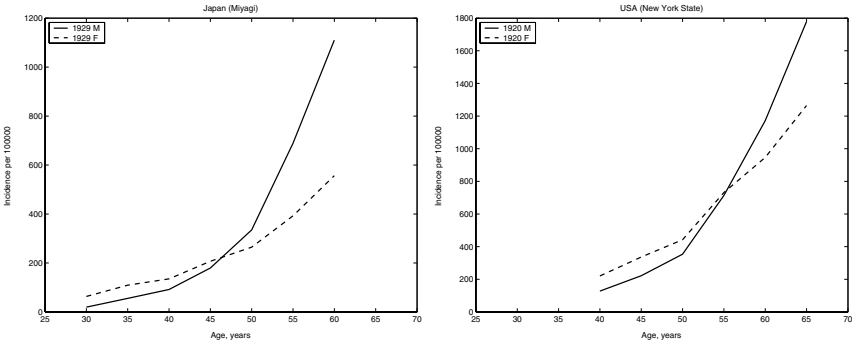

Fig. 2. Female and male "cohort" cancer incidence rates in Japan (Miyagi prefecture), 1929 "cohort" and in USA (New York State), 1920 "cohort". Data source: [3]–[9].

of gender in this process, as well as factors responsible for observed time-trends of these rates. Below, we describe the approach, which has the capability to explain the relative stability of the age pattern of cancer incidence and mortality rates for males and females, as well as their change over time. The approach explores the possibility to represent cancer incidence rate in terms of age-related processes. This involves a new mathematical model of carcinogenesis . This model represents cancer incidence rate as a sum of two components reflecting basic types of age-related changes in an organism (see [15]). We show that in contrast to traditional models of carcinogenesis, the new model, which we call the *ontogenetic* model, captures main features of the age pattern and time-trend of cancer incidence rates. It also explains the relative stability of the intersection pattern of male and female cancer incidence rates. We illustrate this model by the application to data on overall cancer incidence rates in Japan (Miyagi prefecture) (data source: [3]–[9]).

2 Data

We apply our model to data on female and male cancer incidence rates in Japan (Miyagi prefecture). The International Agency for Research on Cancer (IARC) provides the data on cancer incidence in different countries, in seven volumes ([3]–[9]). Each volume covers a time period of several years (usually 3–5 years) for each country (or province and/or ethnic group). The periods vary for different countries. In each volume, female and male average annual cancer incidence per 100000 over the corresponding time period are given for the specific country (province and/or ethnic group), in five-year age groups up to age 85+ (for some countries the first group 0–4 is separated into 0 and 1–4). The data are given for separate sites and for all sites combined. Not all countries are presented in each volume. The longest time series are available

for Japan (Miyagi prefecture). Each of the seven volumes contains the data on cancer incidence in this territory over different time periods. This data set is the foremost one to analyze time trends in cancer incidence rates over time, and is used in this study.

3 Three Components of the Individual Aging Process

Ukraintseva and Yashin [15] suggested studying individual aging by analyzing three internal biological processes that have different age-related dynamics. These include *basal*, *ontogenetic*, and *exposure-related* components. These processes also affect the shape of cancer incidence rate. We assume that any observed age pattern of this rate is the result of the combined influence of these three age-related processes.

The main characteristic of the *basal* component is the age-related decline in the individual rate of living (i.e., in the metabolic and information processing rates). This component is responsible for the deceleration of change in many physiological parameters of an organism with advanced age. It can be responsible for the leveling-off of the morbidity rate at old ages, observed for many chronic diseases (see [15]). This component may also contribute towards the acceleration in rates of onset of *acute* health disorders leading to death (due to deceleration in the potency to recover, and hence due to the progressive decline in individual stress resistance at old ages).

The term *ontogenetic* refers to the developmental history of an organism. The *ontogenetic component* of aging represents effects of metabolic switches accompanying changes in stages of ontogenesis during life (e.g., in infancy, in the reproductive period and at the climacteric). This component of individual aging can be responsible for non-monotonic change in vulnerability of an organism to stress and diseases due to a variation in hormonal balance in an organism. The *exposure-related component* is responsible for long-term accumulation of specific lesions in an organism, which contribute to an increase in the morbidity rate.

A properly balanced combination of all these components may be used for an explanation of age-specific morbidity and mortality patterns in human populations, including cancer morbidity. The obvious advantage of such an approach is that by dividing individual aging into the processes with different age-related dynamics, one has an opportunity to use information from different studies focused on specific aspects of individual aging. For example, the age pattern of ontogenetic vulnerability used in the respective component of cancer incidence rate in our study was obtained from asthma studies (see [12]). A similar pattern is also produced in the studies of other chronic diseases, as shown in [11]. The limitations of this approach are associated with the large amounts of data required for identification of model parameters.

4 The Incorporated Ontogenetic Model of Cancer

To capture the age pattern, time-trends, as well as the intersection of age-specific incidence rates for males and females, we incorporate the three-component model of individual aging [15] into the tumor latency model of carcinogenesis [18]. We specify patterns of age-dependence for different components in the oldest cohort, and set a rule of changing these components from one cohort to the next to construct the corresponding period rates. Following this idea we define cancer incidence rates as

$$\mu_i(x) = \int_0^x h_i(x-t)\, dF(t), \tag{1}$$

where $i = 1 \ldots n$ stands for a cohort, $h_i(x)$ is an age-specific intensity of unrepaired lesion formation in i^{th} cohort, and $F(t)$ is a cumulative probability distribution function of progression times. We suppose that progression times are gamma distributed with fixed shape and scale parameters k and λ and the functions $F(t)$ are the same for all cohorts.

We also assume that the age-specific intensity of unrepaired lesion formation $h_i(x)$ is a result of the combined influence of age-related processes in an organism which are represented by the *basal*, *ontogenetic* and *exposure-related* components described above.

The part of the hazard rate, associated with the *basal* component, should be increasing with the declining rate with age. Respectively, the part of the hazard rate, associated with the *exposure-related* component, should exhibit accelerated increase with age by definition of this component. For the sake of simplicity, we combine the *exposure-related* and *basal* effects and specify one general pattern of hazard rate for these components (referred to as *time-component*). We denote this general component $h_i^{\text{time}}(x)$, where index i is associated with the birth year of the cohort, and x is an individual's age. Thus, the exposure-related lesions in an organism accumulate with age, on the grounds of a basal deceleration in the individual rate of living (e.g., due to general deceleration in information processing) in an organism.

The *ontogenetic* component has a wave-like shape for both males and females, with peaks at early ages and around ages of climacterics for females, and between ages 55 and 65 for males. The peaks correspond to the ages of hormonal imbalance where this component largely influences risks of morbidity and mortality. A similar pattern of morbidity is observed for many human chronic diseases (see [11], [12], [13], [14]). In principle, one can use these patterns to model the *ontogenetic* component. However, these rates, in essence, reflect not only the ontogenetic changes, but also the other factors responsible for the manifestation of the disease. Thus, to model the ontogenetic changes at advanced ages influencing unrepaired lesion formation, we use the function with a pronounced peak around some specific age, and zero otherwise. The peak is around the age of menopause for females, and the pattern is shifted

to the right for males (see Fig. 3). We ignore the peak at early ages for the sake of simplicity. This component is the same for all cohorts.

Denote $h^{\text{ont}}(x)$ the value of the *ontogenetic* component of hazard rate at age x and let $h_0^{\text{time}}(x)$ be the value of the general component (combined from *exposure-related* and *basal* effects) at age x for the oldest cohort. We suppose that the last component may change for different cohorts due to an increasing influence of harmful factors on an organism. The dynamics of this component for i^{th} cohort, $i = 1 \dots n$ is described as

$$h_i^{\text{time}}(x) = (1 + i\ d)\, h_0^{\text{time}}(x)\,, \tag{2}$$

where parameter d characterizes the growth rate of the hazard rate over time. The introduced values $h^{\text{ont}}(x)$ and $h_i^{\text{time}}(x)$ are used to define the age-specific intensity of unrepaired lesion formation for i^{th} cohort, $i = 1 \dots n$, as a sum of these two components,

$$h_i(x) = h^{\text{ont}}(x) + h_i^{\text{time}}(x)\,. \tag{3}$$

5 Application of the Ontogenetic Model to Data on Cancer Incidence Rate by Sex

We apply the model to data on cancer incidence in Japan (Miyagi prefecture) (data source: [3]–[9]). The parameters of the model are fixed at $d = 0.2$, $k = 25$, and $\lambda = 1$. The patterns of the *ontogenetic* component ($h^{\text{ont}}(x)$) and the *time-dependent* component in the oldest cohort ($h_0^{\text{time}}(x)$), for both males and females, are shown in Fig. 3. The trajectories of $h_0^{\text{time}}(x)$ were assumed piecewise constant and were estimated using Matlab's least-square routine.

The observed and estimated male and female incidence rates are shown in Fig. 3.2. Table 1 illustrates the fit of the model. Note that for the sake of simplicity, we used a rather straightforward pattern of $h_i^{\text{time}}(x)$ and a number of fixed parameters of the model. A more elaborated specification of $h_i^{\text{time}}(x)$ and an estimation of all the parameters would likely provide a better fit to the data. However, the message here is that this model captures all the features of the observed cancer incidence rates mentioned above. It describes an increase of the rates over time, the deceleration and decline of the rates at the oldest old ages, and the intersection of male and female incidence rate curves near the age of female climacteric. Increasing $h_i^{\text{time}}(x)$ in cohorts gives an increase of the period incidence rates over time. The specification of a cumulative probability distribution function of progression times and difference in ontogenetic component for males and females produces a decline of the rates at oldest old ages and the intersection of the male and female rates.

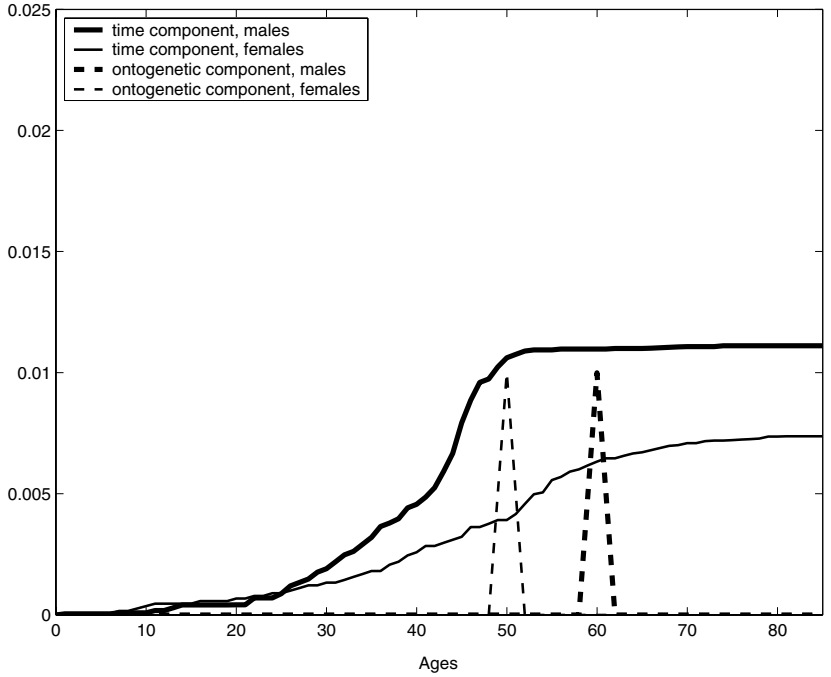

Fig. 3. The ontogenetic model of cancer applied to data on overall cancer incidence rates in Japan (Miyagi prefecture): curves of the combined exposure-related and basal component ("time component") in the oldest cohort and the ontogenetic component for males and females. Data source: [3]–[9].

Table 1. The ontogenetic model of cancer applied to data on overall female and male cancer incidence rates in Japan (Miyagi prefecture): norm of differences (columns 'Norm') and correlation (columns 'Corr') between modeled and observed incidence rates. Data source: [3]–[9].

Period	Norm (Females)	Corr (Females)	Norm (Males)	Corr (Males)
1959–1960	436.105	0.972	384.487	0.990
1962–1964	285.894	0.982	614.039	0.973
1968–1971	211.032	0.993	198.371	0.998
1973–1977	200.417	0.995	502.704	0.994
1978–1981	233.626	0.998	452.061	0.999
1983–1987	94.588	0.999	196.311	0.999
1988–1992	165.258	0.999	201.993	0.999

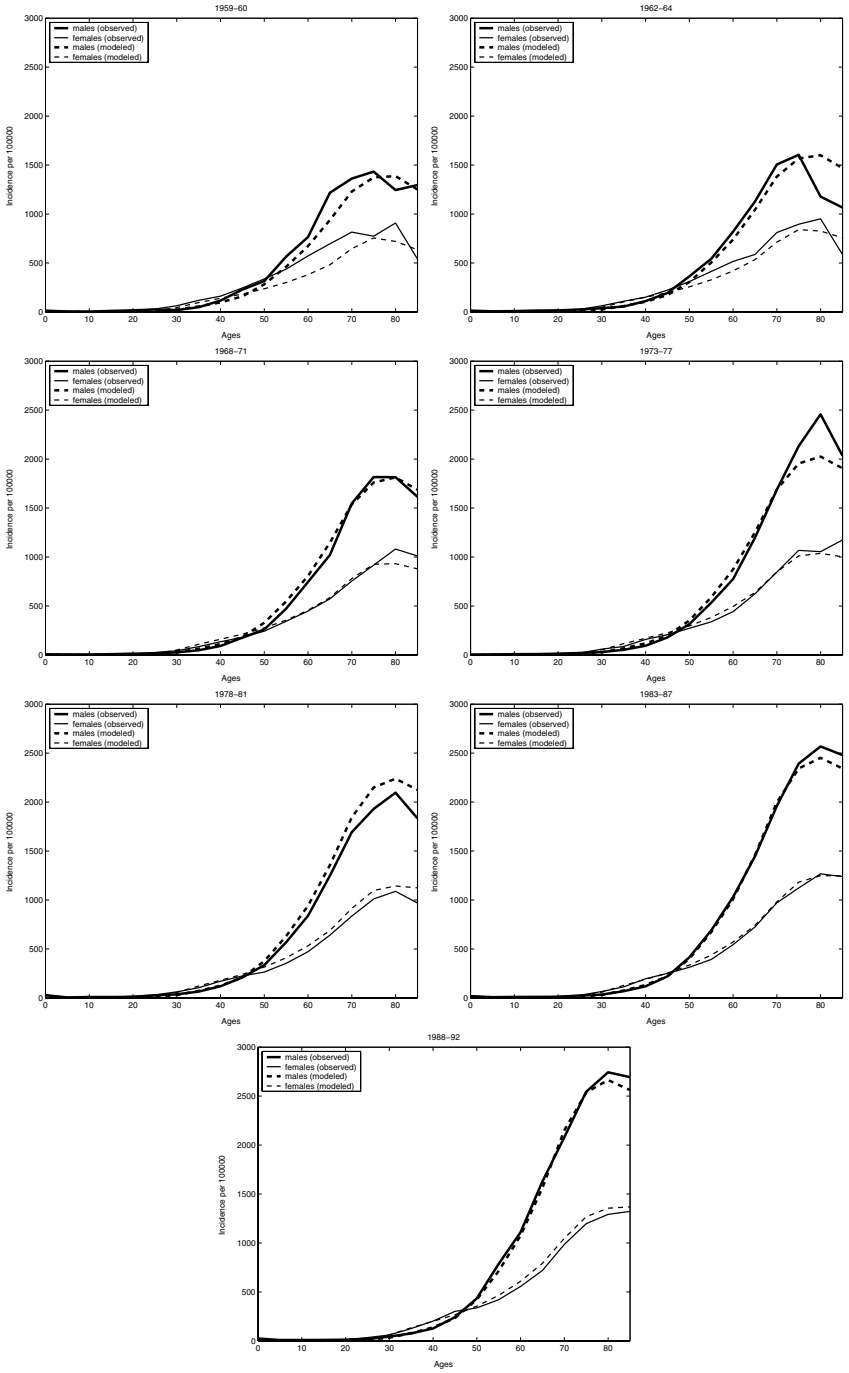

Fig. 4. The ontogenetic model of cancer applied to data on overall cancer incidence rates in Japan (Miyagi prefecture): male and female observed and modeled rates for different time periods. Data source: [3]–[9].

6 Conclusion

The analysis of epidemiological data on cancer shows that cancer became the leading cause of death in most productive ages of human life. The range of ages where cancer maintains its leading role tends to increase with years. In many developed countries the overall cancer incidence rate still tends to increase. Many factors associated with the economic progress could be mainly responsible for the increase in cancer incidence rate. Among those are the improved cancer diagnostics, elevated exposure to external carcinogens such as car exhaust pollution, and factors associated with a Western-like life style (such as dietary habits, new medicines and home-use chemicals). This increase is not likely to be explained by the improvement in cancer diagnostics alone. The survival of cancer patients differs in different countries, despite continuing efforts in sharing medical information on efficiency of cancer treatment procedures and respective drugs.

Different models of carcinogenesis can explain some of the observed phenomena of human cancer incidence rates. The literature on cancer modeling is extensive. The list of classical models includes the multistage model of cancer by Armitage-Doll (AD model), the two-event model by Moolgavkar-Venzon-Knudson (MVK model), and the tumor latency model by Yakovlev and Tsodikov. These models describe biological mechanisms involved in cancer initiation and development, and derive mathematical representation for cancer incidence rate. This representation can then be used in the statistical estimation procedures to test hypotheses about regularities of respective mechanisms and the validity of basic assumptions. The multi-stage model of carcinogenesis [2] explains the increase of the rates over age, but does not describe the entire age-trajectory of cancer incidence rate and does not explain the intersection of male and female incidence rates. The two-mutation model [10], as well as the tumor latency model (see [16], [17]), is capable of describing the entire age-trajectory of cancer incidence rate. However, they cannot explain the stable intersection pattern of male and female cancer incidence rates.

It is clear that the overall cancer incidence rates for males and females do have different age patterns. This conclusion stems from the basic biological knowledge about the difference between male and female organisms. This difference is responsible for the different susceptibility to cancer of certain sites (e.g., breast cancer). The exposure to hazardous materials can also be different for males and females because of their difference in social and economic life. There is, however, neither a theory nor a mathematical model that predicts how age-trajectories of cancer incidence rates will behave, and to what extent these trajectories are affected by environmental and living conditions experienced by populations in different countries.

In this paper we show that the relative difference in age patterns of male and female cancer incidence rates may be explained by the difference in ontogenetic curves of age-dependent susceptibility to cancer for males and females.

This is because the peak of hormonal imbalance in females is between ages 45 and 55, when the reproductive system ultimately stops functioning. In males this peak is shifted to the right (between 55 and 65). The age pattern of cancer incidence rate reflects the contribution of the ontogenetic component of age-related processes in an organism. The heterogeneity in individual frailty may also have a substantial contribution. The ontogenetic model is capable of describing the time trends and the stable pattern of intersection in the male and female incidence rates. In our recent paper [1], we pointed out that the universal pattern of male/female cancer incidence rates might also be a result of different strategies of resource allocation between “fighting" against external stresses and “fighting" against physiological aging used by male and female organisms. This effect needs further explanation, from both biological and mathematical perspectives. The availability of molecular-biological and epidemiological data on stress resistance (e.g., cellular sensitivity to oxidative stress) would allow for the development of more sophisticated mathematical models of such mechanisms. New models are also needed to explain age pattern and time-trends in male/female cancer mortality rates. These models should include information on cancer incidence rates as well as on survival of cancer patients.

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