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BIOLOGICAL AGE AS A CRITERION FOR ASSESSMENT OF THE RISK OF MORTALITY AND MORBIDITY

Kashuba N. A., Melnyk N. A., Sopel O. M.

I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine, Ternopil

Introduction. Currently, most existing approaches to assessing the risk of death or occupational disease in chronic exposure have a number of common shortcomings. Therefore, highlighting the way of using biological age indicators to assess the risk of occupational morbidity is relevant.

The aim of the study is to substantiate the possibility of using data on biological age to assess the risk of developing a disease or death.

Materials and methods of the study. We studied the relationship between the dose of the hazardous factor, biological age and the effect of exposure in 97 men who worked at municipal enterprises and in 112 men (electric welders) in the age range from 21 to 57 years who worked at enterprises of the Ternopil region. The biological age was assessed using a program developed by us.

Results. The article highlights the use of biological age indicators to assess the risk of occupational morbidity. We have proposed a number of mathematical formulas that allow predicting the expected life expectancy based on the data on the value of biological age of workers of different age groups. We have also built a mathematical model of multiple regression, which allows to estimate the partial biological age of workers.

Conclusions. Determination of biological age and its use as an intermediate link in the dose-effect relationship allows to standardize the study group, to exclude the distorting effect of unaccounted for or unknown factors on the dose-effect relationship, to judge the predominant direction of the effect on the body of the factor under study in dynamics.

Key words: biological age, morbidity, mortality, death rate, disease, dose, effect

Introduction

Currently, most existing approaches to assessing the risk of death or occupational disease in chronic exposure have a number of common shortcomings. On the one hand, a real assessment of health risks is impossible without a sufficient information base on the quantitative and qualitative characteristics of risk factors, on the other hand, due to insufficient information on the health status of workers [1–2]. However, conducting mass epidemiological studies in our country is associated with a number of difficulties. The assessment of the impact in the dynamics of occupational factors on the sanitary and hygienic characteristics of working conditions proposed by some authors [3–4] is often impossible due to frequent and diverse restructuring of production, termination or change of ownership, staff turnover, etc. Assessment of the health status of the study cohorts based on the results of periodic medical examinations and, especially, on the level of morbidity with temporary disability [5–6] is also far from objective. In private companies, many workers refrain from taking sick leave for fear of losing their jobs. In connection with the provision of paid medical services, periodic medical examinations have become the subject of commercial relations, which affected the quality and reliability of information about the state of health.

It is known that there are problems of a more general nature at work. As a number of authors [7–10] point out, quantitative risk indicators (mortality, morbidity) always reflect the complex impact

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on a person not only of production factors, but also of the environment, lifestyle, social and household factors, individual risk factors (heredity, bad habits). Therefore, when risk assessment is focused on a particular environmental factor, there is always a possibility that other, equally important factors will not be taken into account. Because of the war, the possibility of applying mathematical analysis, in particular factor analysis, which allows to assess the nature of the interaction of factors and its contribution to the studied quantitative risk indicator, is sharply limited, and the probability of error in risk assessment increases.

For example, according to some data [11], when assessing the risk of cardiopulmonary pathology from exposure to welding aerosols in welders of shipyards working in metal closed structures, the fact that they work in geomagnetic field shielding conditions was not taken into account. The control sample included workers who were not only unexposed to welding aerosols, but also were not affected by the absence of the geomagnetic field, which affects the central nervous and cardiovascular systems. Obviously, the relative risk assessment in this case will be incorrect.

From the point of view of some specialists, the search for level-time-effect relationships is impossible due to the lack of a generally accepted methodological apparatus for establishing cause-and-effect relationships environment-health and due to the impossibility of taking into account the whole variety of combinations of exposure to harmful factors on the body and, accordingly, variants of adaptive physiological reactions to this effect of the worker's body [12–13].

As noted earlier, one of the significant risk factors is heredity and genetic predisposition to the development of certain diseases. At the same time, the genetic component of human health is an exclusively individual value that fluctuates significantly, which in itself is an insurmountable obstacle to taking this factor into account in epidemiological studies. However, in some cases, the genetic factor of health significantly affects the results of risk assessment. Thus, during periodic medical examinations when hiring (in our case, electric welders), in accordance with the list of contraindications to work in dusty conditions, persons with signs of respiratory pathology are screened out. Therefore, electric welders who have just started working are obviously healthier in terms of respiratory organs than workers of the control sample, where, due to the absence of adverse effects of welding aerosols, the state of respiratory organs was not regulated. Moreover, in a number of cases, persons who have not undergone medical examinations for admission to work at welding facilities join labor collectives where there are no harmful factors affecting the respiratory system. As a result, the difference between the level of genetically determined respiratory health of workers of the compared groups increases.

The situation is complicated by another circumstance. As noted by some authors [14–15], there is a significant fluctuation in the value of relative risk in different seniority groups. At the same time, this phenomenon is less pronounced in older seniority groups than in younger ones.

As our research has shown, this is due to the fact that at the beginning of employment, some workers are dismissed from hazardous work due to the development of respiratory diseases. Thus, at the workplace there is a constant selection of persons least susceptible to respiratory diseases. This is especially typical for persons with short work experience.

As a result, workers of each subsequent seniority group have initially a higher genetically determined reserve of vital resistance of respiratory organs.

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Obviously, all the above circumstances significantly affect the assessment of relative risk.

The aim of the study is to substantiate the possibility of using data on biological age (BA) to assess the risk of developing a disease or death.

Materials and methods of the study

We studied a group of 97 men who worked at municipal enterprises and a group of electric welders (112 men) in the age range from 21 to 57 years, who worked at the enterprises of Ternopil region. The study was conducted with biomarkers reflecting the state of the cardiovascular, respiratory and central nervous systems. The data of mortality tables were used. Dust load was determined by the amount of dust deposited in the respiratory organs during the period of direct contact with welding aerosol.

Statistical processing of the materials and construction of mathematical models was carried out using applications implemented in software packages SPSS 16, Statistica 12.0, EXCEL, as well as with the help of our own programs. Estimation of biological age was carried out using the program created by us (Figure).

Results of the study and their discussion

Age is one of the most important risk factors for the development of pathology and mortality. One of the most convenient mathematical models is the Gompertz-Makem equation, which describes the exponential dependence of population mortality on age. In fact, this equation is:

$$(Ro = K + R \cdot exp^{at}) \qquad (1)$$

describes the general law of entropy increase in living systems, which allows to consider the risk of death from the standpoint of mathematical analysis as the degree of entropy increase in a living system over time.

During the standardization of comparable seniority groups it is assumed that the age factor in this case is already taken into account. In fact, this is quite true. In the seniority groups, especially the

Figure. Program for estimating biological age

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younger ones, there are often persons with the age significantly exceeding the average calendar age of this group.

In addition, it is known that the calendar age (CA) is not adequate enough to assess the risk of morbidity or mortality due to age-related changes, because external and internal factors affecting the human body can accelerate the aging process, and therefore increase the risk of morbidity and mortality. And in this case, BA more adequately reflects the rate of aging, the probability of disease and death.

All of the above indicates the need to find new methodological approaches to assess the risk of occupational diseases and mortality in chronic exposure.

In our opinion, the determination in risk assessment by studying the nature and strength of the dose-BA-effect relationship instead of the dose-effect relationship allows solving a number of these problems.

Assessment of the relationship between dose and BA allows to evaluate the integrated impact of age, individual factors (heredity, habits), environmental factors, including for each worker individually.

Moreover, the impact of harmful factors of the occupational environment is reflected in the BV integrally, taking into account their specific impact.

Obviously, individuals of the same CA, who have been exposed to the same dose of the factor under study and have the same or similar values of BA, have also been exposed to the same integral impact of other adverse factors (social, individual, etc.). As a result, the formation of the study cohort by the value of BA leads to its standardization by unaccounted factors of influence. The control group is formed in the same way. Establishing the relationship between dose and effect through BA allows to exclude the adverse effect of unaccounted or unknown factors on this relationship.

Since BA reflects the availability of vitality reserves, it is the most accurate criterion of the risk of death or disease. At the same time, it integrally reflects the entire cumulative impact of adverse factors on the human body.

The presence of groups with different CA and the same BA at the same dose of exposure indicates a different susceptibility of workers to the harmful factor, or (and) that they are exposed to different intensity of the integrated impact of environmental factors outside the production. In the first case, it is possible to determine the age susceptibility to the active factor, which allows to establish the dose – age – effect relationship. Consequently, this opens up new opportunities for risk management by establishing the dose – BA – effect relationship.

For example, there is a certain well-known relationship between dose and BA. When studying the BA of workers at any enterprise with a given dose of exposure, it may turn out that the average BA value is higher than the level of previously established BA at other similar enterprises with the same dose of exposure. Obviously, at this enterprise there is a certain factor or group of factors that additionally affect the BA. Based on the known relationship between the BA and the effect, an amendment to the expected effect can be made. This approach also allows to estimate the contribution of the occupational hazard (dose) and an additional unknown factor to the risk. It is extremely important that RfD is a method of pre-nosological diagnosis, which allows timely correction of risk management mechanisms before the effect occurs.

Application of the dose – BA – effect relationship allows in some cases to avoid complex and time-consuming epidemiological studies.

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The above Gompertz-Makem formula (1) after a number of transformations can be transformed into the mathematical model proposed by A. L. Reshetiuk:

$$q = \exp [A(T/(T_{max} - 1))] \quad (2)$$

to determine the BA of the population [16–17]. Coefficient A is considered by the author as a component of background mortality associated with environmental impact. It reflects the average Meikem's coefficient and the exponentially increasing decrease in the stability of a living system with age.

Substituting the established value of BA of the risk group instead of T, which is the calendar age of the study population, into the formula, we obtain the mortality rate for this age group. Thus, it is possible to determine the expected mortality rate, depending on the value of BA, by building a mathematical model. We have proposed a model for determining the life expectancy (LE). In our case, a mathematical model was built to determine the life expectancy of the population of Ternopil region on the basis of data on the mortality rate of the population of this region, which is described by the linear regression equation:

$$E_x = 12.24 - 6.38 \cdot A_p \cdot (T_{ip} / T_{max} - 1), \quad (3)$$

where E_x – life expectancy, A_p – background component of mortality for Ternopil region, T_{ip} – mortality rate of a certain age group of the region, T_{max} – maximum life expectancy.

Also, a mathematical model of the working life expectancy for workers of car repair enterprises and car service stations was built based on the data on the value of the BV of workers of different age groups:

$$E_{xт} = 12.24 - 6.38 \cdot A_{ht} \cdot (T_{ih}/T_{max} - 1), \quad (4)$$

where E_{xt} is the life expectancy of workers, A_{ht} is the background component of mortality for workers of this enterprise, T_{ih} is the CA of workers, T_{max} is the maximum LE of the population. (The methodology for determining the values of A_p and A_{ht} is presented in [18–19]).

In our case, LE of electric welders in comparison with the population of the region was less by (7.7 ± 0.06) years in the seniority group up to 10 years and by (11.4 ± 0.1) years in the practice groups over 20 years.

The peculiarity of the proposed method is the possibility of determining the LE in the absence of data on the mortality rate of the study group. Thus, having a known dose and, as a result of its action, the corresponding BA, it is possible to calculate the effect, while avoiding long studies of the mortality rate in the study group.

Obviously, in this case, it is difficult to judge the role of a specific factor that contributes to the increase in the value of BA, since the latter integrally reflects the influence of all environmental factors. Therefore, when studying the effect of welding aerosols, in addition to the integral value of biovolume ($BA_{(I)}$), we also determined its partial value to determine the effect of welding aerosols on the BA of the cardiopulmonary system. To do this, we have built an appropriate mathematical model of multiple regression, which allows us to estimate the partial biological age (PBA) [20–21].

In this case, those biomarkers were selected that reflect the state of those organs and systems (cardiopulmonary and central nervous systems) that are exposed to the adverse effects of welding production factors. Studies have shown that the PBV of the cardiopulmonary system significantly exceeds the $BV_{(I)}$ integrally. This is especially observed at high doses, where there is a failure of adaptation and disruption of compensatory mechanisms. In particular, for persons over 35 years of age, the cardiopulmonary partial biological age

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(PBA) is determined by the following linear regression equation:

$$PBA = 105.0764 + (-0.31723 \cdot ADC) + (0.072141 \cdot ADD) + (-0.46433 \cdot LE) + (-2.14663 \cdot ORT) + (-0.02895 \cdot SB) \quad (5)$$

In our case, the PBA exceeded the integral $BA_{(I)}$ for workers with 0–4 years of experience by (1.2 ± 0.03) years. In some cases, the PBA was less than the $BA_{(I)}$, which may be explained by careful selection of persons for compliance with the cardiopulmonary system during preliminary medical examinations at employment. In the group of more than 20 years of experience, the PBA exceeded the $BA_{(I)}$ by (5.6 ± 0.06) years. Having data on mortality of the population, in our case from cardiopulmonary diseases, and PBA, it was not difficult to calculate the partial influence of occupational factors on the LE using the formula 1, 2.

Comparison of PBA and $BA_{(I)}$ allows to assess the contribution of welding aerosols both to the general processes of reducing the vitality of the whole organism and those organs and systems that are most susceptible to adverse effects. Based on the statistical data on the dependence of the level of general morbidity and cardiopulmonary morbidity of the population of the study region on age and replacing the value of the latter with the values of $BA_{(I)}$ and PBA of the study cohort, it is possible to judge the influence of occupational factors on the level of general and cardiopulmonary morbidity. Therefore, for the study cohort, the ratio $CS = PBA / BA_{(I)}$ can be considered as the ratio of the risk of cardiopulmonary and general morbidity, where CS is the ratio of the average values of the biovolume of the study cohorts.

A similar ratio for the study cohort (CR) can be obtained from actual morbidity data. The presence of a significant difference in the obtained coefficients will allow us to judge about the presence of an error in the estimation of BA or in the collection of information on the incidence based on the results of medical examinations. In our case, the difference in percentage terms between CRBA and CS was 12.7 %, which indicates a good correspondence of indicators. Of great importance for risk assessment and management is the dynamics of changes in CSBA. If its value decreases with increasing dose, it can be assumed that the overall impact of the factor on the body is predominant. The increase in the value of the coefficient as the dose increases allows us to think about the strictly directed effect of the factor on those organs and systems that are most susceptible to its influence. In our case, there was an increase in CSBA (by 6.1 %) with increasing dose, which suggests a more pronounced effect of welding aerosols on the cardiopulmonary system.

In our opinion, the following coefficients are also interesting:

$$K_{(I)} = BA_{(I)} / KA \text{ and } K = BA / KA, \quad (6)$$

where $K_{(I)}$ and K are the corresponding coefficients.

Conclusions

Determination of biological age and its use as an intermediate link in the dose-effect relationship allows:

- to standardize the study group;
- to exclude the distorting effect of unaccounted or unknown factors on the dose-effect relationship;
- to judge the emergence of new, previously non-existent, disturbing factors;
- in some cases to determine the expected future life expectancy of a certain cohort without complex epidemiological studies;
- to judge the predominant direction of the influence of the studied factor on the body in the dynamics.

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ORCID ID of co-authors and their contribution to the preparation and writing of the article:
Kashuba M. O. (ORCID ID 0000-0002-3370-280) – formulation of the idea, key goals and objectives, data interpretation, writing the article, drawing conclusions;
Melnyk N. A. (ORCID ID 0000-0002-7357-7551) – literature search and analysis, collection of primary data, writing the article, design of the text;
Sopel O. M. (ORCID ID 0000-0003-3807-1317) – literature search and analysis, writing the article, drafting the text.

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Contact person: Kashuba Mykola, MD, Professor, Department of General Hygiene and Ecology,
I. Horbachevsky Ternopil National Medical University, 1, Maidan Voly, Ternopil, 46001. Tel.: + 38 0 97 228 43 84.
E-mail: kashuba@tdmu.edu.ua