
The impact of middle age on the viability of patients with nonmalignant and malignant diseases

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Abstract: Deep myelosuppression, an officially sanctioned effect of non-selective cytotoxic cancer therapy, would be expected to be incompatible with mounting of a powerful host defense against spontaneous malignancy. To explore this theoretical difficulty, we used middle age as a natural model of a temporary decline in lymphocytopoiesis, caused by physiological thymus involution. The impact of middle age on the levels of death from nonmalignant and malignant diseases was analyzed retrospectively, using population health data from Europe (the European Network of Economic Policy Research Institutes, 1995); the UK (Statistics Team at the Cancer Research UK, and the Office for National Statistics cancer survival rates for 2007-2010), and the USA (National Center for Health Statistics, 1987-2007; National Vital Statistics System, 1999-2010; National Cancer Institute's Surveillance, Epidemiology, and End Results [SEER], 1992-2010). The rate of death and survival used to check whether the vectors of middle age-specific changes of these parameters are opposite or coincident in cancer patients and those with certain non-malignant somatic diseases. According the temporary trend on a middle- age portion of plot, the curves were graded negative or positive (+ = viability is not change or goes up; - = viability goes down). Comparisons of aggregate data showed that middle age exerted opposite effects on the health of those with cancer and non-malignant diseases. In middle age, serious health conditions, such as some cancers, are easier to treat, but the overall quality of life is reduced by various morbidities, especially infections. The comparing of the impact of middle age on the viability of patients with nonmalignant and malignant diseases in alternative terms of immunity or morphogenesis leads to recognition of trophic contribution of thymus into tumor development. By analogy, we assume that use of cytotoxic therapy can exert indirect benefit, thus compromising hemato- lymphocytopoiesis.

Keywords: Death Rates, Malignancy, Middle Age, Mielopoiesis, Populations

1. Introduction

Age-related decline in immune function (an immunosenescence) is very commonly noted negative factor in medical practice [1]. Loss of thymic function is thought to contribute to weaker immunosurveillance by the elderly, increasing the instance of cancer, autoimmune diseases, and infections [2]. The permissible extent of myelosuppression by cancer therapy, in terms of the lowest limit of lymphocytopenia [3], is comparable to that of those who survived nuclear bomb attacks [4]. To better understand this phenomenon, and to explore the mechanism by which myelosuppressive cancer therapy is of benefit, we used natural thymus involution as a model of a “therapeutic” influence. Such involution remains an evolutionary mystery; it is not induced by senescence. The lymphoid parenchyma of the organ commences involution at a young age, and involution is

complete by middle age [5]. As the thymi of most patients over 40 years of age lack naive T cells [6], bone marrow becomes the main source of lymphoid stem cells and T-cell precursors [7]. Physiological dislocation of T-cell production from the thymus to the bone marrow is accompanied by a temporary distortion of the continuous decline in leucopoiesis, manifested by different signs. These are temporary decrease in the levels of immature lymphocytes in blood [8, 9], a smaller mean packed volume of blood cells [10], a pause in the age-specific reduction in leucocytes telomere length [11], and stabilization of the mitotic index in the epidermis (which had steadily increased since birth) [12]. It is noteworthy that, in the 15 years since Chernobyl, middle-aged clean-up workers (n = 12,310) have experienced more newly diagnosed somatic diseases than did those in other age groups [8]. Unexpectedly,

middle-aged patients with breast cancer (n=83,536) died more slowly than those who were older or younger [13]. These data [8-13] reveal an opposite influence of middle age on human health, but it is difficult to explain such “middle-age phenomenon” on the basis of immunity. If the immune system were in play, health changes in patients with and without cancer would be unidirectional, as the defense system is involved in the detection and destruction of bacteria, viruses, and cancer cells (immunosurveillance) [14]. To check at the population level whether the vectors of middle age-specific health signs are opposite or coincident in cancer patients and those with certain non-malignant somatic diseases.

Objectives: To check at the population level whether the vectors of middle age-specific health signs are opposite or coincident in cancer patients and those with certain non-malignant somatic diseases.

2. Data and Methodology

The data were obtained from six cohorts:

2.1. Cohort A

Original data on death rates (per 100,000 subjects), from eight leading causes, in 10 5-year age groups of the white population of the United States in 1999-2010, obtained from [15]. Death rates were analyzed by the age groups: 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, and 60-64 years. The causes of death included in analysis were: malignant neoplasms (C00-C97); diseases of the heart (I00-I09, I11, I13, I20-I51); cerebrovascular diseases (I60-I69); human immunodeficiency virus (HIV)-caused diseases (B20-B24); diabetes mellitus (E10-E14); chronic liver diseases and cirrhosis (K70,K73-K74); viral hepatitis (B15-B19); influenza and pneumonia (J09-J18); septicemia (A40-A41); and nephritis, nephrotic syndrome, and nephrosis (N00-N07, N17-N19, N25-N27).

2.2. Cohort B

Morbidity rates for influenza and pneumonia per 1,000 white persons in the United States (of both sexes), in 2007, obtained from [16]. Morbidity rates were analyzed by the age groups 5-17, 18-44, 45-65, and 65+ years.

2.3. Cohort C

Death rates from HIV-caused diseases in Hispanics of the United States (both sexes) in 1987-2007, obtained from [17]. Death rates were analyzed by the six age groups: 5-14, 15-24, 25-34, 35-44, 45-54, and 55-64 years.

2.4. Cohort D

Original data on the predicted probabilities of chronic illness, by age, in European countries of high socio-economic status (Belgium, Denmark, Finland, Germany, Sweden, and the UK), in 1995, obtained from [18]. We calculated the average values of the impact of age on the incidences of chronic illness, using aggregate data, by sex, employing 13

5-year age groups: 21-25, 26-30, 31-35, 36-40, 41-45, 46-50, 51-55, 56-60, 61-65, 66-70, 71-75, 76-80, and 81-85 years.

2.5. Cohort E

Original data on 5-year net relative survival, by age, of British cancer patients diagnosed between 2007 and 2010 (both sexes), obtained from [19]. We combined patients with 15 different cancers into three groups exhibiting different survival rates, and analyzed the data by six age groups: 15-39, 40-49, 50-59, 60-69, 70-79, and 80-89 years. Group 1 included cancers of the bowel, female breast, prostate, testis, uterus; and malignant melanoma. Group 2 included cancers of the male larynx, the cervix uteri, ovary, and kidney. Group 3 included cancers of the esophagus, stomach, pancreas, lung, and brain.

2.6. Cohort F

Similar original data were obtained from SEER, in the USA, [20] and used as a referent for cohort E. Five-year relative survival rates, by age at diagnosis, between 1992 and 2010, were calculated for white (including Hispanic) patients, of both sexes, with 20 types of invasive cancers. We combined all cancers into four groups, and used five age-groups for each: <20, 20-49, 50-64, 65-74, and 75+ years. Group 1 included cancers of the colon and rectum, male and female breast (separately), prostate, bladder, testis, bones and joints. Group 2 included cancers of the larynx, cervix uteri, ovary, and kidney. Group 3 included cancers of the esophagus, stomach, liver, pancreas, and lung. Group 4 consisted of patients with chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), and acute myeloid leukemia (AML).

2.7. Statistics

In our observational study the middle age-related death or morbidity curves were generated for each group, performing curve fitting in Excel [21]. We defined a single function that will best describe the data points. Often higher-order polynomial approximations were necessary to adequately describe the trend in the data, obtaining a line that has a satisfactory R^2 value. Coefficient of determination R^2 is a statistical measure of how close the data are to the fitted regression line. The maximal value of the R^2 was used for the assessment of goodness of fitting of the function to the data. Regression t-test confirmed R-value, by probability p-value [22]:

$$t = \sqrt{[R^2 (n-2) : (1 - R^2)]} \quad (1)$$

A significant polynomial curves made the interpretation less intuitive. The equations for the lines, however, did not need for us to interpret the data. According the temporary trend on a middle- age portion of plot, the curves were graded negative or positive (+ = viability is not change or goes up; - = viability goes down). We compared the grade of curves (+ or -) for groups of patients with and without malignancy to realize whether the grades coincide or not.

3. Results

3.1. Death and Morbidity Rates by Age

Special health features of middle-aged populations with and without cancer are compared in Fig. 1.

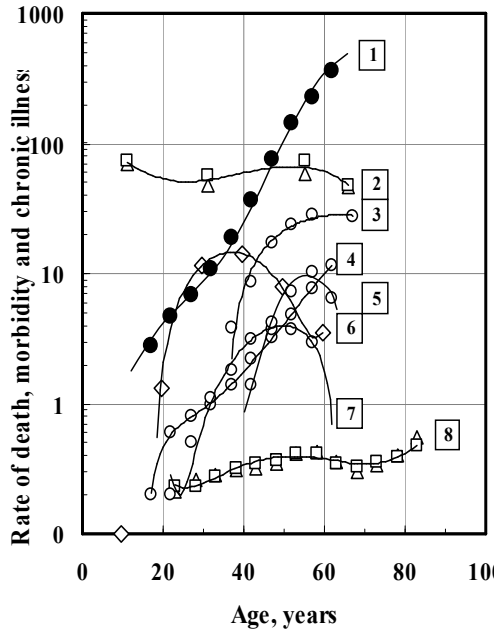


Figure 1. Health features of middle-aged populations with and without cancer in Cohorts A, B, C, and D.

x- age (in years); this is the midpoint of each age interval;
y- rate of deaths per 100,000 subjects, or rate of morbidity per 1,000 subjects, in the specified groups.

Curves 1, 3, 4, 5, and 7 (circles) show the death rates of white US subjects (both sexes) in cohort A from: 1) malignant neoplasms (black), 3) chronic liver disease and cirrhosis, 4) influenza and pneumonia, 5) viral hepatitis, and, 7) human immunodeficiency virus (HIV) diseases. Curve 2 shows the morbidity rates of white US subjects with influenza and pneumonia among males (triangles) and females (squares) in cohort B. Curve 6 (the rhombi) shows the death rates from HIV diseases in cohort C (Hispanics in the USA; both sexes). Curve 8 shows the predicted rates of chronic diseases among males (triangles) and females (squares) of Northern Europe (cohort D; relative units are used). The approximating equations and the probabilities of approximated lines were: 1) fifth-order polynomial, $R=0.999\pm 0.005$, $p<0.001$; 2) third-order polynomial, $R=0.905\pm 0.173$, $p=0.002$; 3) second-order polynomial, $R=0.987\pm 0.081$, $p<0.001$; 4) fifth-order polynomial, $R=0.999\pm 0.003$, $p<0.001$; 5) second-order polynomial, $R=0.93\pm 0.22$, $p=0.024$; 6) fourth-order polynomial, $R=0.999\pm 0.020$, $p=0.001$; 7) third-order polynomial, $R=0.991\pm 0.055$, $p<0.001$; and 8) fifth-order polynomial, $R=0.977\pm 0.064$, $p<0.001$.

Fig. 1 shows that, in subjects 25-60 years of age, the death rates and morbidities from certain somatic and infectious diseases became higher, whereas the death rates from malignant diseases fell slightly.

The ratios of death rates from malignant diseases to the death rates from various nonmalignant diseases were also temporarily lowered in those aged 30-50 years (Fig. 2).

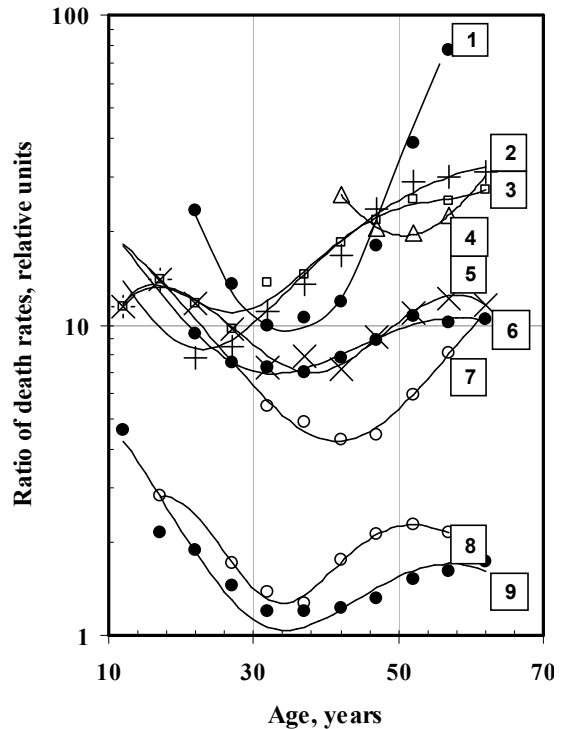


Figure 2. The ratios of death rates from malignant diseases to death rates from various nonmalignant diseases, during middle age, in Cohort A.

x- age (in years); this is the midpoint of each age interval;
y- the ratios: rate of deaths from malignant diseases / death rates from various nonmalignant diseases. All the rates are per 100,000 subjects.

Curves 1-8 show ratios for the US population of cohort A. In all cases, the numerator is the death rate from malignant neoplasms (C00-C97). The denominators in the ratios of curves 1-8 are death rates from 1) human immunodeficiency virus (HIV) disease (B20-B24); 2) influenza and pneumonia (J09-J18); 3) septicemia (A40-A41); 4) viral hepatitis (B15-B19); 5) cerebrovascular diseases (I60-I69); 6) diabetes mellitus (E10-E14); 7) chronic liver disease and cirrhosis (K70, K73-K74); 8) *nephritis, nephrotic syndrome, and nephrosis (N00-N07, N17-N19, N25-N27); and, 9) diseases of the heart (I00-I09, I11, I13, I20-I51). The approximating equations and probabilities of approximated lines were: 1) fourth-order polynomial, $R=0.999\pm 0.001$, $p<0.001$; 2) fourth-order polynomial, $R=0.989\pm 0.053$, $p<0.001$; 3) fifth-order polynomial, $R=0.991\pm 0.043$, $p<0.001$; 4) second-order polynomial, $R=0.998\pm 0.046$, $p=0.002$; 5) fourth-order polynomial, $R=0.979\pm 0.68$, $p<0.001$; 6) third-order polynomial, $R=0.975\pm 0.083$, $p=0.001$; 7) second-order polynomial, $R=0.989\pm 0.057$, $p<0.001$; 8) fifth-order polynomial, $R=0.996\pm 0.037$, $p<0.001$; and, 9) third-order polynomial, $R=0.965\pm 0.087$, $p<0.001$. *-the ratio is reduced 10-fold.

Some diseases do not feature in Fig. 2, for the following reasons. We could not calculate minimum ratios using data on chronic lower respiratory diseases (J40-J47). For in situ neoplasms, benign neoplasms, and neoplasms of uncertain or unknown behavior (D00-D48), valid rates of death are guaranteed only for subjects aged <30 and >65 years. Valid death rates from essential hypertension and hypertensive renal disease (I10, I12, I15), aortic aneurysm and dissection (I71), atherosclerosis (I70), anemias (D50-D64), Parkinson's disease (G20-G21), Alzheimer's disease (G30), and certain other diseases, were not available for all age ranges.

3.2. Survival of Cancer Patients by Age

Signs of the “middle-age” phenomenon were evident in the survival data of cancer patients. Figure 3 shows the 5-year relative survival levels of British (Cohort E) and US cancer patients (Cohort F), by age. In both cohorts, the data are organized into only a few groups. Each group contained cancer sites exhibiting minimal survival differences by age. This allowed us to minimize the SEs of average survival values (S) within groups, thereby facilitating detection of age-specific differences between groups (Fig. 3).

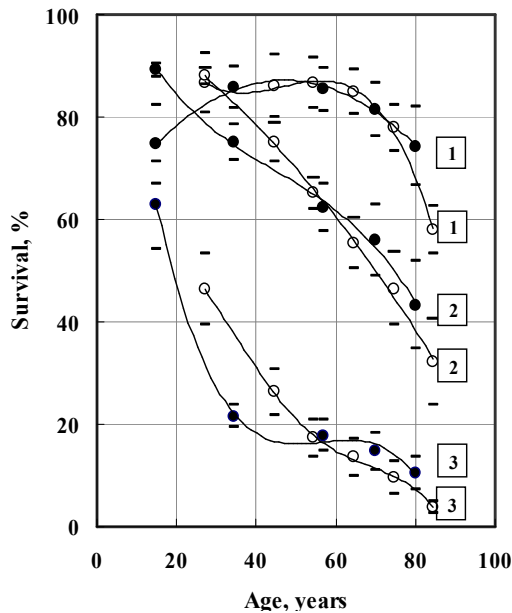


Figure 3. Five-year survival of cancer populations by age at diagnosis; Cohorts E and F.

x- age (in years); this is the midpoint of each age interval;
 y- relative survival of patients with solid cancers at different sites (S ± SE), %.
 Cohort E: empty circles; Group 1 included cancers of the bowel, female breast, prostate, testis, uterus; and malignant melanoma. Group 2 included cancers of the male larynx, the cervix uteri, ovary, and kidney. Group 3 included cancers of the esophagus, stomach, pancreas, lung, and brain.
 Cohort F: black circles; Group 1 included cancers of the colon and rectum, male and female breast (separately), prostate, bladder, testis, bones and joints. Group 2 included cancers of the larynx, cervix uteri, ovary, and kidney. Group 3 included cancers of the esophagus, stomach, liver, pancreas, and lung.
 The approximating equations and probabilities of approximated lines were: Cohort E, (group 1): third-order polynomial, R=0.998±0.023, p<0.001; (group 2): second-order polynomial, R=0.999±0.022, p<0.001; (group 3): fourth-order polynomial, R=0.999±0.011, p<0.001. Cohort F, (group 1): second-order polynomial, R=0.997±0.045, p<0,001; (group 2): third-order polynomial, R=0.998±0.034, p<0.001; (group 3): third-order polynomial, R=0.999±0.027, p<0.001.

Fig. 3 shows that patients with group 1 diseases, in both cohorts E and F, exhibited slight improvements in survival between 35-55 years of age. Temporary retardation of declining survival by age was specific to group 3. Such improvement, or stabilization of susceptibility to cancer therapy during middle age, in groups 1 and 3, was more obvious for the US population (Cohort F), which was much greater than the UK population (Cohort E). No cancer site in group 2 of either Cohort E or F exhibited the “middle-age”

phenomenon.

It was important to determine the extent to which the survival of patients with systemic malignancies at different ages differed from that of patients with solid neoplasms.

Figure 4 shows the relationship between survival of solid malignancies in groups 1 and 3, described above (Fig. 3) for Cohort F, and survival of group 4 patients with different leukemias (Cohort F).

The observed visual concordance of the dotted lines for cancers and the solid lines for lymphocytic leukemia were verified, at high probabilities (p values) using equations:

$$S_1 = 0.51 S_c \pm 39.4, R=0.99 \pm 0.08, p=0.006 \quad (2)$$

and

$$S_3 = 10.3e^{0.0212 S_a}, R=0.99 \pm 0.06, p<0.001 \quad (3)$$

where: S₁ and S₃ are the survival rates of groups 1 and 3 with solid neoplasms, in % values; and S_c and S_a the survival rates in group 4 patients with CLL and ALL, respectively.

The probabilities afforded by similar equations (not shown) fitting CML and AML data were much lower: p=0.05 and 0.04. The similarities of the curves for lymphocytic leukemia and solid neoplasms point to a possible role for lymphocytopoiesis in survival of patients with cancers at the sites included in groups 1 and 3 of cohort F.

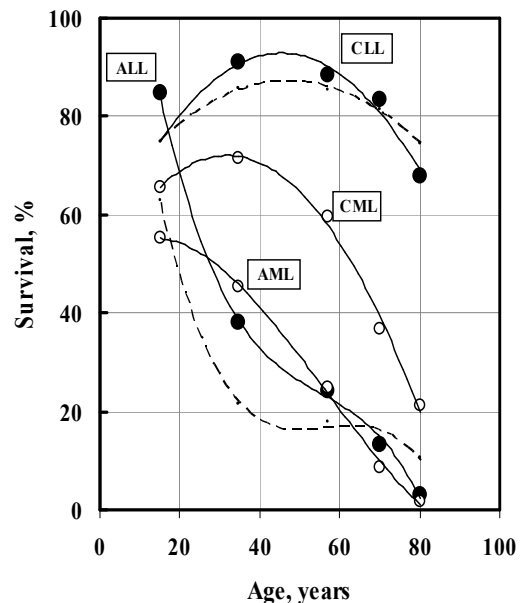


Figure 4. The relationships between 5-year survival in patients with leukemias and solid neoplasms, in Cohort F.

x- age (in years); this is the midpoint of each age interval;
 y- relative survival levels of those with different malignancies (S), %.
 Dotted lines: solid neoplasms in Groups 1 and 3 (shown earlier in Fig. 3);
 Solid lines: leukemias in Group 4; black circles: chronic lymphocytic leukemia CLL and acute lymphocytic leukemia ALL, empty circles: chronic myeloid leukemia CML and acute myeloid leukemia AML. The approximating equations and probabilities of the approximated lines for group 4 were: CLL: second-order polynomial, R=0.984±0.127, p=0.02; ALL: third-order polynomial, R=0.999±0.021, p<0.001; CML: second-order polynomial, R=0.996±0.048, p<0.001; AML: third-order polynomial, R=0.999±0.023, p<0.001. Statistics for the dotted lines are given in Figure 3.

4. Discussion

Our retrospective analysis of specific population health parameters yielded results in agreement with our preliminary data, which supported an opposite influence of middle age on human viability in those with certain malignant or nonmalignant diseases [8, 13]. Among nonmalignant illnesses, which may manifest such interdependencies, the most significant were diseases of the heart, cerebrovascular diseases, chronic liver disease and cirrhosis, nephritis, nephrotic syndrome and nephrosis, diabetes mellitus, influenza and pneumonia, viral hepatitis, human immunodeficiency virus (HIV) diseases, and septicemia (Figs. 1 and 2). The most probable sites of neoplasms involved in the supposed interactions are the bowel, colon, rectum, breast, prostate, testis, esophagus, stomach, pancreas, lung; and CLL and ALL. (Figs. 3 and 4).

The presence of infections and lymphocytic leukemias in these lists proves that the middle-age anomaly reflects hemato-lymphocytopoietic status. However, any explanation of the temporary retardation of cancer activity in middle age via depletion of so-called immune regulatory T-cells [23-25] is not convincing. Increased nonmalignant morbidity, together with a risk of death from infection, is the concomitant background, which is rather incompatible with the expected activation of defense systems. Moreover, some malignant sites, such as the larynx, cervix uteri, ovary, kidney, and others, are not involved in the phenomenon, pointing to an influence of histotype. Thus, the histotypes of various targeted organs may determine the reproduction, in bone marrow, of circulating tissue-committed stem cells and other T-cells that function in morphogenesis [26-30].

In contrast to an explanation involving immunity, the ability of morphogenic cells originating from the bone marrow to support cellular renewal in *both normal and malignant tissues* seems to be a preferable explanation of the results obtained. For example, the rise in the levels of dead, but not viable, CD45-CD31-CD146+ T-positive endothelial precursors when a tumor is present exhibits a highly significant positive correlation with the response to anti-angiogenic therapy, and patient benefit [31]. Indeed, a temporary pause in tissue renewal may *reduce both* tumor aggressiveness and the resistance of normal tissues toward infection; this is what our data show.

The entire practice of cytotoxic cancer therapy affords an alternative explanation of the “middle age” phenomenon. Any myelosuppressive action of modern combined chemotherapy is not rare or random; 85% of the most commonly used drugs are myelosuppressants [32]. The permissible level of hemato-lymphotoxicity during cancer therapy is very deep when either selective (local) radiotherapy or non-selective chemotherapy is used to treat cancer [3]. Such a similarity emphasizes that the extent of cellular deficiency in blood must be induced if a positive clinical result is to be obtained [33].

Moreover, high-dose *local* radiotherapy can damage tumor cells lethally, but non-selective chemotherapy cannot. Otherwise, chemotherapy would be fatal to the organism as a

whole. Nevertheless, chemotherapy is sufficiently effective to be widely used. The mechanism of non-selective chemotherapy is supposed to be indirect, causing only temporary disturbances in cellular reproduction [34]. Similarly, chronic exposure of the whole body to low-dose radiation, which is not enough to directly destroy a tumor, may benefit approximately 10,000 people in Taiwan, greatly reducing the incidence of cancer deaths (to about 3 per cent of the incidence of spontaneous cancer death in the general Taiwan population) [35,36].

Thus, we suggest that a natural reduction in lymphocytopenia during middle age may improve the survival of cancer patients by a similar indirect mechanism. Such a mechanism is most likely to be manifest if cancer treatment features a suboptimal balance between efficiency and myelotoxicity. Under such circumstances, any limitation of therapeutic toxicity may be part-balanced via natural suppression of lymphocytopenia in middle age.

Our study has limitation. It is retrospective study of a widely varied patient populations. We are unable to exclude the possibility that unequal distribution of unidentified clinicopathologic parameters in our patient cohorts may have biased the observed result. Future work should explore this alternative mechanism, in view of the practical importance thereof.

5. Conclusion

Comparisons of aggregate data showed that middle age exerted opposite effects on the health of those with some cancers and non-malignant infectious diseases in terms of the rates of death, morbidity, and survival. In middle age, serious health conditions, such as some cancers, are easier to treat, but the overall quality of life is reduced by various morbidities, especially infections. The comparing of the impact of middle age on the viability of patients with nonmalignant and malignant diseases in alternative terms of immunity or morphogenesis leads to recognition of trophic contribution of thymus into tumor development. By analogy, we assume that use of cytotoxic therapy can exert indirect benefit, thus compromising hemato-lymphocytopenia.

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