Scientific Research Publishing

Open Journal of Biophysics, 2025, 15(1), 1-17
https://www.scirp.org/journal/ojbiphy
ISSN Online: 2164-5396
ISSN Print: 2164-5388

Physiological Variance of CD34 Marker's Content in Twenty Tissues Determining Different Risks of Cardiovascular Diseases and Cancer in Them

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How to cite this paper: Shoutko, A.N. and Karamullin, M.A. (2025) Physiological Variance of CD34 Marker's Content in Twenty Tissues Determining Different Risks of Cardiovascular Diseases and Cancer in Them. *Open Journal of Biophysics*, **15**, 1-17.
https://doi.org/10.4236/ojbiphy.2025.151001

Received: October 5, 2024
Accepted: December 2, 2024
Published: December 5, 2024

Abstract

The decreasing of hazard ratio for cancer incidence (HR_{CVD}) in the range of twenty native tissues (lung, liver, brain, hematologic, neuroendocrine renal, pancreas, lymphoid, bladder, colon, lip-oral-head-neck, leukocytic, rectum and anus, thyroid, soft tissue, prostate, skin, ovarian, breast, uterine) as much, as decreasing of the level of cardiovascular pathology (CVD) in the host before malignization, have been described by C.F. Bell *et al.* in 2023. Earlier, in 2022, the decreasing of 5-year mortality from cancer in similar range of tissues discussed by us as the inverse dependence from the content of stem CD34 markers in tissues before malignization, with example of population in England. In present article we investigate the interrelation between both data more thoroughly, using accessible and more representative populations level of the data. The analysis shows that high level of HR_{CVD} is able to predicts only high cancer death for tissue sites in the beginning of the range, being applied to the referent data of cancer cases and deaths in estimated population of USA 2024. Along with this, an increasing the content of CD34 stem marker in the native tissues of the same range was favorite for increasing of cancer's cases at the end of the range, diminishing, in parallel, the signs of vasculo-endothelial pathology, *i.e.* HR_{CVD}. Thus, the cases (incidence) of cancer depend directly rather from content of CD34, which preexisted in native sites, than that from HR_{CVD}. Further analysis shows that CD34 content averaged over twenty cites dominates over that CD2 marker of total T-cells more than 7 times, in oppose to their ratio in the blood. The enhancement of stem CD34 marker in the range of tissues is accompanied by unidirectional rising of its maturing derivatives, vasculo-

endothelial CD31 and total T-cells CD2 markers, which contents relate positively to increasing of cancer death in US population 2024. The increase of CD34 decreases cancer mortality (death: cases) in sites, but indirectly, rather due to enhancement of the denominator. The high HR_{CVD} (more than 1.0) in range of 20 tissues, concerns of those of them, which have had highest mitotic activity (by Ki67), but lowest "stemness" (by CD34), "vascularity" (by CD31), cancer's incidence (cases) and the worse results of therapy. Oppositely, the normal tissue with lowest HR_{CVD} (below 1.0) and Ki67, but highest CD34, CD31, and cancer incidence (cases) are more sensitive to treatment. Thus, the residential hematopoietic "stemness" in native tissues acts as natural protectors for cardio-vascular system and promoter for cancer incidence in them. The steady and irreversible exhaustion of current regenerative resource (CRR) of BM, which assumed by us as a product of CD34 number and average telomeres length, manifests itself in acceleration of non-malignant CVD and deceleration of malignancy in population +70 (in term the death per 10^5), according to data extracted from WHO Mortality Database. The similar deficit of CD34 arises artificially during cytotoxic treatment of cancer, when rapid waste of local CRR forces malignant cells to search more "stemness" cites. The competition between malignant and native tissues of the host for scanty CRR seems to be the most important factor for evaluation and prediction of prevalence, curability, and long-term results in oncology.

Keywords

Population, Cardiovascular Pathology, Cancers, Interrelation, Tissues, CD Markers, Prognostic Value, Revision

1. Introduction

The recent studies have confirmed that anti-tumor therapy causes CVD with different risk among of cancer sites [1] [2]. In turn, the treatment of CVD increases the tumors incidence [1] [3]. The patients with atherosclerotic CVD (aCVD) had higher hazard ratio of cancer's incidence (HR_{aCVD} = 1.2), than those without (naCVD), with HR_{naCVD} = 1.11. Furthermore, the both HR_{aCVD} and HR_{naCVD} are decreasing along with the range of potential cancer's sites: lung, liver, brain, hematologic, neuro endocrine, renal, pancreas, lymphoid, bladder, colon, lip-oral-head-neck, leukocytic, rectum and anus, thyroid, soft tissue, prostate, skin, ovarian, breast, uterine [4]. This selectivity has been associated by authors with processes of inflammation, adaptation in tissues, in particular with protein CD47 in blood, which is signal "don't-eat-me" to macrophages, *i.e.* blocker of efferocytosis, by which phagocytic cells are removed the apoptotic cells [3]. Earlier we demonstrated the quantitative increasing of survival of patient's with cancers in similar range of tissues along with the increasing of natural content of the marker CD34 and CD31 in them before malignization [5]. As these markers are associated with vasculo-angiogenesis, they could be involved in variability of the cancer's HRs

described in [4]. Another word, the different levels of risk of malignization in tissues could be result not of CVD as such [4], but some favorite properties of the hematopoietic stem cells marker CD34 or its descendants contributed in malignization of native target tissues, as we expected. The main goal the present investigation was to clarify this opportunity.

2. Methods

2.1. Preparing the Data Extracted from [1] for Further Analysis

The top-down layout of the tissues corresponds to average declining of cancer incidence in them by term hazard ratio (HR_{CVD}) proposed by authors [4] on the base of preexisted cardio-vascular diseases (CVD). For correct statistic assumption, we made slight rearrangement of these original data for each cancer site in both ranges of HR (with atherosclerosis HR_{aCVD} and without it HR_{naCVD}). After rearrangement the sites in both ranges has got the same number (nm.) from the first 1 to the last 20: 1-lung, 2-liver, 3-brain, 4-hematologic, 5-neuroendocrine, 6-renal, 7-pancreas, 8-lymphoid, 9-bladder, 10-colon, 11-lip oral-head-neck, 12-leukocytic, 13-rectum and anus, 14-thyroid, 15-soft tissue, 16-prostate, 17-skin, 18-ovarian, 19-breast, 20-uterine. The both corrected ranges were approximated by us with exponential functions. The composition and sequence of the lines of tissues sites, had kept fixed throughout of present study. All relations in article have approximated by different functions generated in Excel automatically, keeping the line of tissue sites fixed, without any additional rearrangement.

2.2. Testing of HR_{CVD} Prognostic Properties

As the people in the control subgroup without CVD (noCVD) in [4] were younger, than those in subgroups with CVD (of 18 - 39 years vs. of 45 - 59 years old), it had to be seen, how far could this imbalance affect received results. To examine the influence of age-related disbalance in [4], we test first the prognostic properties of HRs from [4] on extracted from [6] newly estimated by U.S. Census Bureau the cases ($\times 10^{-5}$) and the death ($\times 10^{-5}$) in 2024 for range of cancer sites, needed as a referent one, representing total $335{,}893 \times 10^6$ of entire U.S. population. Thus, the data extracted from both original sources were used in our modification.

2.3. Examination of Hematopoietic Protein Markers in Different Normal Tissues

In parallel, we examined the dependence of cancer case and death in the range of tissues [6] from native content of different hematopoietic CD markers in them. These global data tabulated in [7] in term "consensus" ones. They were used in modification proposed by us earlier [5]. It consists in a conversion of each consensus value of marker (i) in tissue (z) into the ratio (relative unit, r.u.), normalized to the marker's value for bone marrow (iBM). The parameter (iz:iBM) permits to evaluate real content of each marker in different tissues, ignoring the

errors related to detection of different (i) in different (z). The primary level of transcribed mRNA molecules (nTPM) for each of eight CD proteins in each of twenty organs were normalized preliminary to the corresponding nTPM in bone marrow (BM). Each relative unit, r.u., corresponds one of eight CD-proteins and one of twenty tissues. The average relative unit M in twenty normal tissue cites (n = 20) for each of eight single markers formed the line: 7.3 of CD34, 3.9 of CD25, 3.2 of CD133, 1.6 of CD31, 1.0 of CD2, 0.41 of CD47, 0.16 of Ki67, and 0.1 of CD247. So, the CD34 marker dominates in tissues, and the CD247 (unmatured T-cells) is least represented quantitatively.

By same manner we investigate the relation of CD markers in tissues from [7] and HRs from [4].

2.4. Generalization of the Main Links of Proteins of Normal Tissues with Future CVD and Malignization

Finally, all newly received data were combined and discussed with comprehensive conclusion. Therefore, we would like to contribute the new arguments in the problem of selective influence of CVD on incidence of cancer in different tissue sites, basing on the data received by us earlier [5] [8]-[11].

The eight protein markers for each of twenty tissue/organ included: marker of proliferation Ki67, hematopoietic stem cells CD133 and CD34, Treg CD25, vascular CD31, total T-cells CD2, CD47 and CD247. All of CD247 indicate young post-thymic T-cells, which function is still unclear, because they often are discussed as a contributing to the suppression of immune surveillance, antitumor activity, and contributing to neoplastic progression [12]. They unite γ, δ T-cells, T-reg, naive CD4 T-cells, NK Tcells, memory CD8 T-cells, MAIT T-cells, double D4+ CD8+, CD4− CD8−, naive CD8 Tcells, memory CD4 T-cells.

2.5. Statistical Analyses

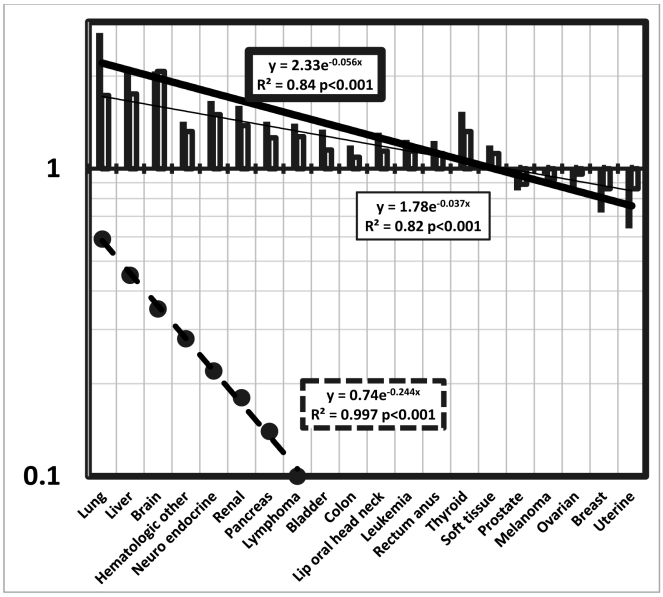
Individual parameters were evaluated statistically with the calculation of the mean value M, standard deviation (SD) and standard error (SE). The average values of M were compared using the t-test and the probability of p. The data compared by mean value (M), standard deviation (SD), standard error (SE), t-criterion and probability p. The trends of the aggregate parameters evaluated by mathematical functions generated automatically in the Excel program. The coefficient of determination R^2 used as a statistical measure of the goodness of fit of the regression line to the data. R^2 confirmed by Equation (2) for its t -parameter:

$$t = R^2 \times (n-2) \times (1-R^2) \tag{1}$$

3. Results

3.1. The Test of Prognostic Validity of HR from [4]. Preparing the Data Extracted from [4] for Further Analysis

Figure 1 presents the data extracted from [4] in our modification.



Abscissa: line of twenty tissue's sites as the potential targets for malignization. Ordinate: Hazard Ratios (HR) of patients with naCVD, or aCVD vs. 27.11×10^6 individuals without CVD (no CVD). Black columns are for HR_{aCVD}, white columns—for HR_{naCVD}. Formulae of exponential approximation for both HR_{naCVD} and HR_{aCVD} by of target's sites are shown in the boxes: thin solid line is for HR_{naCVD}, solid thick line is for HR_{aCVD}. Black points are for $d = (\exp HR_{aCVD} - \exp HR_{naCVD})$.

Figure 1. Hazard ratio HR of cancer incident in different tissues during one year after diagnosis nonatherosclerotic CVD (naCVD, $n = 21.43 \times 10^6$), or atherosclerotic CVD (aCVD, $n = 2.24 \times 10^6$).

According exponential approximations, the both ranges of all cancer's HRs are diminishing from lung site (x = 1) to uterine site (x = 20). According the formulae in the boxes, the maximum of HR for lung cancer (x = 1) in subgroups with atherosclerosis (HR_{aCVD}) is greater than in subgroup HR_{naCVD} (2.33 vs. 1.78) as well, as the rate of exponential reduction of HR per each site number (−0.056 vs. −0.037). The independent additional "atherosclerotic" HR ("d") has maximum 0.59. The exponential rate of reduction of "d" is −0.24 per one cancer site, *i.e.* more than 6 times vs. rate −0.037 for HR_{naCVD}.

Thus, highest reduction's rate of the atherosclerotic component of malignization $d = 0.59e^{-0.24x}$ (in bi-exponential formula $HR_{aCVD} = d + 1.78e^{-0.037x}$) leads to its quick declining, which covered only 6 - 7 first sites (lung, liver, brain, lymphoid, hematologic, neuro endocrine). The HR for last 7 sites in the range of 12 - 20 (thyroid, soft tissue, prostate, melanoma, ovarian, breast, uterine) declines faster at atherosclerosis (HR_{aCVD}) than exponential rate −0.037 per one cancer site, which is typical for HR_{naCVD}. This our brief interpretation of original data extracted from [4] was developing according argument given in **Methods** 2.1.

3.2. The Test of Prognostic Validity of HR from [4] with Cases and Death in People of US Population

Table 1 presents the results of testing HR with big data [6]. The estimated new

cancers cases and deaths in adult population of US for the current calendar year 2024 [6] had distributed with new model methodology for range in twenty sites, which are identical to the same shown on Figure 1, and interrelations of parameters evaluated by approximation in Excel program (Table 1).

Table 1. The evaluation of applicability of the HRs proposed in [4], to the estimated cancer cases and death of twenty sites in the adult population of US 2024 [6].

y = f(x)*	y, per10^3 per1year		
x	y = Cases 2024 = f(x)	y = Deaths 2024 = f(x)	y = Mortality = (Death/cases) = f(x)
HR_{naCVD}	$y = -126.3\ln(x) + 122.9$ $R^2 = 0.12$, p = 0.12	$y = 23.12x + 23.36$ $R^2 = 0.04$, p = 0.38	$y = 0.372x - 0.127$ $R^2 = 0.26$, **p = 0.02**
HR_{aCVD}	$y = -43.6\ln(x) + 110.6$ $R^2 = 0.031$, p = 0.43	$y = 29.18x - 12.57$ $R^2 = 0.27$, **p = 0.02**	$y = 0.2x + 0.06$ $R^2 = 0.19$, **p = 0.05**
HR_{CVDa}:HR_{naCVD}	$y = 34.6e^{0.662x}$ $R^2 = 0.017$, p = 0.56	$y = 94.75x - 74.86$ $R^2 = 0.32$, **p = 0.008**	$y = 0.27x + 0.046$ $R^2 = 0.037$, p = 0.38
$d = HR_{aCVD} - HR_{naCVD}$	$y = 64.96e^{0.652x}$ $R^2 = 0.037$, p = 0.38	$y = 75.52x + 17.7$ $R^2 = 0.45$, **p <0.001**	$y = 0.21x + 0.31$ $R^2 = 0.051$, p = 0.33

*The different mode of approximation (linear, exponential, or logarithmic) have preconditioned by best level of probability p for found relation. The valid equations are shown by bold fonts.

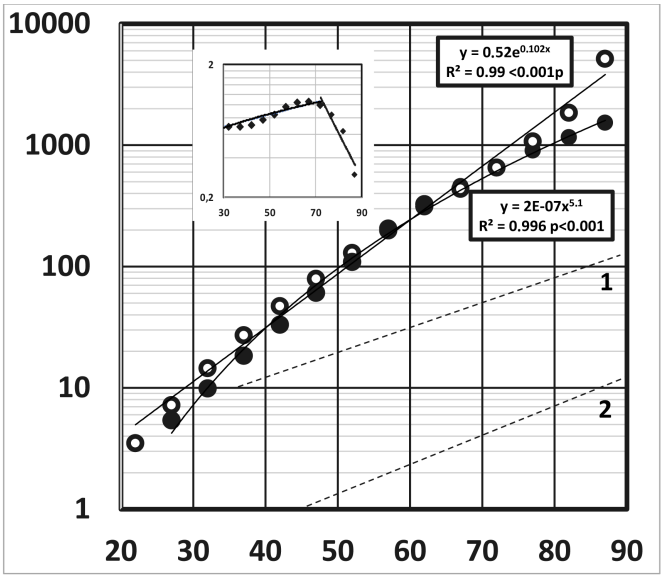
First result of the test is, that the numbers of the estimated cases (incidence) in US population 2024 in different sites do not fit the both types of HR as well, as their derivatives ($d = HR_{aCVD} - HR_{naCVD}$) and (ratio HR_{aCVD}:HR_{naCVD}).

The fail of all of them to prognose the numbers of cancer cases 2024 in general US population seems logic, because only 9.9% adult Americans have CVD (without hypertension) [13], whereas small population of 2.7×10^7 used in [4] was enriched with CVD as fare as 21% without hypertention too (coronary artery disease, peripheral arterial disease, cerebrovascular disease, heart failure, valvular disease, and congenital heart disease, and atrial fibrillation). Moreover, the proportion of people with a CVD used in [4] was enriched up to 8.2%, in comparing with aCVD incidence 0.1% - 0.6% persons-year estimated in US middle-aged adults [14].

Second incorrection is the younger control subgroup noCVD vs. subgroups with CVD, in term of the percentage of the people +70 years old [4]. The distributions of age, built by us according data given in [4], shows the excess people +70 in common CVD subgroup (18.8%) over control noCVD (1.7%). The entire adult population of US have people +70 about 5% (4.5 ÷ 5.5) only [15], that is much closer to 1.7%, than to 18.8%.

Figure 2 shows the example of strong relation between the death rate from cancer and from CVD (per 10^5 people) by age in US population 2000 [16]. This natural correlation may simulate the false dependency of cancer incidence from HR in [4] due to disbalance of age distribution in control noCVD and in the both

CVD subgroups. Thus, the authors of [4] used the subpopulations with artificially enhanced content CVD and cancer death in older people tested vs. younger control noCVD. Consequently, they could interpret wrongly the nonspecific (age-related) increasing of the both incidence cancer and CVD, as a causal relationship between them.



Abscissa: age, years. Ordinate: number of the death per 10^5 people per one year. The formulas of approximation are in the boxes, each box touches to the parts of curve, which it describes. White circles are for CVD, black circles -for cancer. Dotted line: estimated prevalence of carotid plaque (1; $y = 1.206e^{0.0524x}$, $R^2 = 0.93$, $p < 0.001$) and carotid stenosis (2; $y = 0.063e^{0.0581x}$, $R^2 = 0.94$, $p < 0.001$) by age, percentage of global population [17]. An inset shows the ratio (deaths rates from cancer to CVD' death rate) as function of age.

Figure 2. Cancer and CVD death rate per 10^5 people in adult population of US 2020 by age group [16].

The positive dependence of estimated deaths 2024 [6] on atherosclerosis HR_{aCVD} and derivates of [4] in **Table 1** reflects the regularity shown on **Figure 2** also. Thus, the excess of patients +70 years old in subgroup CVD [4] can be a cause of age-related increasing both cases CVD and cancer death as well, which was wrongly accepted as a result of CVD, not the age. It explains the absent of applicability HR_{CVD} from [4] to estimated cases of cancer in the test-population 2024, which is free from artificially enriched part of +70 people (**Table 1**). Thus, our investigation confirms only the positive predictive power of atherosclerotic CVD, *i.e.* HR_{aCVD} from [4], for number of estimated cancer's death in the range of twenty sites of the test-population US 2024 [6].

3.3. Examination of Hematopoietic Protein Markers in Different Normal Tissues

However, the analysis completed above, does not clarify the reasons for different sensitivity of organs to malignization, relation of malignization with cardio-vascular

pathology, and prevalence of deadly atherosclerosis in sites at the beginning the range shown on Figure 1.

A range of tissues, similar to shown on Figure 1, we analyzed and discussed earlier in term of fifth years cancer's survival in population of England [5]. We first argued the necessity to analyze of markers originated from bone marrow in different normal tissues instead their presence in the blood. The range of survival in sites turned out to be dependent to the content of CD 34 and CD31 in the sixteen tissues [5]. Partially, it was shown, that the lack of "CD34-stemness" and "CD31-vascularity" in liver, lung, esophagus, pancreas, and stomach shortens the time of local growth of future tumors in them, and bring closer a transition of logarithmic type of malignant biomass development into slower quasi-linear one, characterized with concomitant hypoxia, followed metastases, and death at lower survival [10]. Oppositely, higher preexisting level of CD34 and CD31markers in such normal tissues as bladder, breast, prostate, testis, thyroid, uterus predestined the better 5years survival in populations of England, delaying metastasis. The likeness of two cancer site ranges in two articles gave us opportunity to check an applicability our vision of resident CD-markers inside of normal tissues as the universal predictors both a cancers and CVDs level, in term of HR.

The numbers of twenty sites used in present investigation, relates quantitatively to only one of eight CD marker, namely stem CD34, which increases along with number of sites, from lung (nb.1) to the uteri (nb.20):

$$\text{CD34 r.u.} = 0.45 \times \text{nb.} + 2.62,\ R^2 = 0.25,\ p = 0.02 \quad (2)$$

The equation shows, that the less of CD34 in normal tissue is, the worse curability of cancer in it, and vice versa.

Table 2 shows the calculated relation of some hematopoietic markers, chosen us earlier [5], with HR and estimated cases of 2024 by range of main tissue's sites, as the potential targets for specific cancers. The data Table 2 does not confirm the optimism about the prognostic perspectives of CD25 positive Treg [18]. Other marker of normal tissues CD47, which is the signal "don't-eat-me" to macrophages [3], does not involved in CVD, or spontaneous malignization in the range of investigated sites, at least statistically.

Table 2. Dependence of estimated cases 2024 [6] and HR [4] on natural content of hematopoietic markers [7] in normal tissues.

	y				
x	HR_{aCVD}	HR_{naCVD} y = f(x)	dHR = $HR_{aCVD} - HR_{naCVD}$	Cases 2024	Mortality 2024 (Deaths: Cases)
CD34	$y = 1.58e^{-0.028x}$ $R^2 = 0.17$, p = 0.06	$y = 1.4e^{-0.028x}$ $R^2 = 0.20$, **p = 0.05**	$y = -0.07\ln(x) + 0.19$ $R^2 = 0.2$, **p = 0.05**	$y = 0.0756x + 0.44$ $R^2 = 0.21$, **p = 0.04**	$^*y = 0.52x^{-0.43}$ $R^2 = 0.25$, **p = 0.02**
CD25	$y = 0.14\ln(x) + 1.27$ $R^2 = 0.05$, p = 0.31	$y = 1.157x^{0.049}$ $R^2 = 0.03$, p = 0.45	$y = 0.0731\ln(x) + 0.1$ $R^2 = 0.06$, p = 0.29	$y = 0.7181x^{0.1367}$ $R^2 = 0.026$, p = 0.5	$y = 0.2163x^{0.15}$ $R^2 = 0.03$, p = 0.45
CD31	$y = 0.049x + 1.3$ $R^2 = 0.024$, p = 0.55	$y = -0.097\ln(x) + 1.3$ R^2 = 0.06, p = 0.29	$y = 0.14\ln(x) + 0.1$ $R^2 = 0.15$, p = 0.09	$y = 0.3318x + 0.4729$ $R^2 = 0.25$, **p = 0.02**	$^{**}y = 0.28x^{-0.41}$ $R^2 = 0.13$, p = 0.12

Continued

CD2	$y = 1.25e^{0.037x}$ $R^2 = 0.022p = 0.56$	$y = -0.02\ln(x) + 1.24$ $R^2 = 0.005$, p = 0.77	$y = 0.077\ln(x) + 0.22$ $R^2 = 0.12$, p = 0.12	$y = 0.9476x^{0.322}$ $R^2 = 0.23$, **p = 0.035**	**y = 0.07x + 0.26 $R^2 = 0.21$, **p = 0.04**
CD133	$y = -0.022x + 1.45$ $R^2 = 0.034$, p = 0.45	$y = -0.017x + 1.3$ $R^2 = 0.048$, p = 0.32	$y = -0.006x + 0.15$ $R^2 = 0.01p = 0.71$	$y = 0.6933x^{0.0934}$ $R^2 = 0.0316$, p = 0.45	***y = − 0.09ln(x) + 0.36 $R^2 = 0.36$, **p = 0.0025**
CD47	$y = -0.153x + 1.44$ $R^2 = 0.006$, p = 0.78	$y = 1.22e^{-0.023x}$ $R^2 = 0.001$, p = 0.92	$y = -0.127x + 0.18$ $R^2 = 0.016$, p = 0.56	$y = 0.691e^{0.0593x}$ $R^2 = 0.0003$, p = 0.98	$y = 0.223e^{0.334x}$ $R^2 = 0.011$, p = 0.71
CD247	$y = 1.606x^{0.087}$ $R^2 = 0.11$, p = 0.15	$y = 1.341x^{0.042}$ $R^2 = 0.055$, p = 0.33	$y = 0.06\ln(x) + 0.3$ $R^2 = 0.12p = 0.13$	$y = 0.8675x^{0.0808}$ $R^2 = 0.0167$, p = 0.59	****y = $0.4358x^{0.212}$ $R^2 = 0.13$, p = 0.12
Ki67	$y = -0.05\ln(x) + 1.2$ $R^2 = 0.024$, p = 0.96	$y = -0.05\ln(x) + 1.1$ $R^2 = 0.05$, p = 0.9	$y = -0.023x + 0.14$ $R^2 = 0.01$, p = 013	$y = 1.034x^{0.118}$ $R^2 = 0.049$, p = 0.97	$y = 0.383x^{0.1258}$ $R^2 = 0.06$, p = 1.07

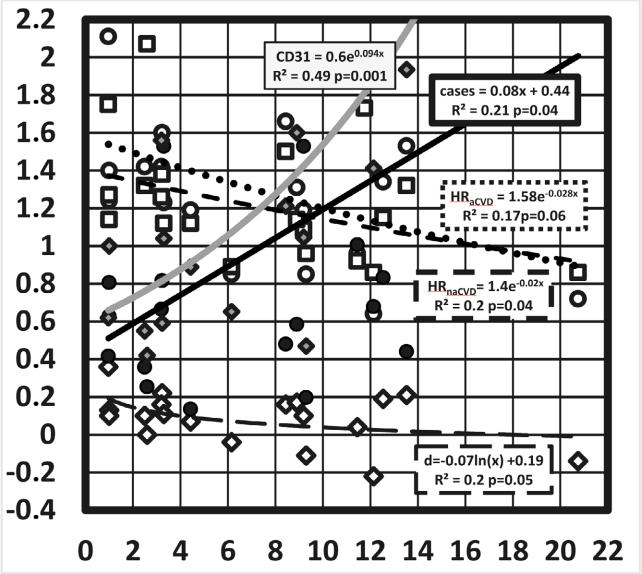
⊖ The formulas have chosen according the best probability of an approximations of the four used: by linear, logarithmic, exponential, or power functions. The minus before "x" in formulas means its opposite quantitative association of "y" with "x". The valid equations are shown by bold fonts. The mode of changing mortality: * by increasing of the cases, for CD34; **by increasing of the death for CD31 ($y = 0.124x + 0.084$, $R^2 = 0.34$, p = 0.007);** by increasing of death for CD2 ($y = 0.27x^{0.50}$, $R^2 = 0.35$, p=0.007); ***by insignificant decreasing of the death, for CD133; **** by insignificant increasing of the death, for CD247.

According to Table 2, a number of CD34 marker in tissues declines HR_{naCVD} and atherosclerotic component $d = HR_{aCVD} - HRn_{aCVD}$ (p = 0.05), *i.e.* heals the vascular pathology, but promotes the cancer cases (p = 0.04). The hematopoietic "stemness" CD34 in tissues induces initial growth in situ, because the number of cancer cases (incidence) 2024 becomes proportional to tissues' content of stem marker CD34 (p = 0.04). Thus, "stemness" CD34 only **simulate** the decline of relative mortality by increasing of numbers of cases, *i.e.* denominator in fractional number "death: cases".

The CD31 acts similar way with cases, but increase the deaths also. Thus, CD34 originated from BM in the healthy tissues, *i.e.* the CD34 "stemness" is a promotor of incidence new cases of cancer, but a protector for CVD. CD31" vascularity" in combination with CD34 only, is responsible for cancer death. Vascular endothelium marker CD31 associates with CD34 directly in endothelial cells, being a descendants of stem cells. It tends in tissues closer to the stem CD133 and CD34, than the "immune-competent, protective" T-cells marker CD2. For instance, a CD31 tissue's content depends on CD2 less probable ($y = 1.46x^{0.29}$, $R^2 = 0.21$, p = 0.04), than on CD34 values ($y = 0.6e^{0.094x}$, $R^2 = 0.49$, $p < 0.001$).

Figure 3 illustrates the main results of the Table 2.

The decreasing of HR_{CVD} associates with increasing of CD34 in tissues, and accompanies by multiplying of new cases of cancer, that points on favorite influence of "stemness" on both cardiovascular and malignant tissues. The increasing of CD31 with CD34 along with decreasing of HR_{CVD} confirms the protective role of CD31 in genesis of atherosclerosis [19]. The pattern of atherosclerosis ($HR_{aCVD} - HR_{naCVD}$) at the beginning of tissues range disappears further, as CD34 and CD31 increases in favorite sites at the end of range with excess of CD34 in prostate, ovarian, breast, and uteri. Moreover, both atherosclerosis and CVD are obviously suppressed at these sites due to higher content of CD34 in them.

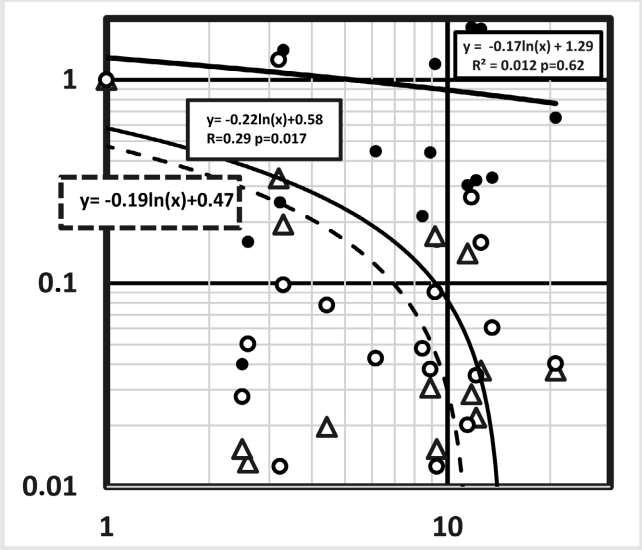


Abscissa: natural CD34 content in tissues, relative units. Ordinate: HR_{aCVD} (dotted line, open circles), HR_{naCVD} (short-dashed line, squares), ($HR_{aCVD} - HR_{naCVD}$) long-dashed line, rhombuses, from Figure 1, and cancer cases(black solid line, black circles) from Table 2. The CD31-gray solid line, gray rhombuses. Formulae for approximation (Table 2) are in the boxes with corresponding frame.

Figure 3. Association of HR_{CVD} and cancer incidence with the natural CD34 tissue's content.

The number of CD2 (total T cells population) increases together with the number of cancer cases ($p = 0.035$; Table 2) and the number of death ($p = 0.007$), that is the shock for doctrine of immune cells defense against cancer. The content of CD2 relate positively with progenitor marker of "vascularity" CD31 ($y = 0.46x^{0.72}$, $R^2 = 0.21$ $p = 0.04$), and young T-cells CD247 ($y = 2.5199x^{0.62}$, $R^2 = 0.57$, $p < 0.001$. Thus, the function of sub-fractions of CD 2 and CD247 young post thymic T cells seems rather protumor, though it used to associate with essential role in adaptive immune response [7].

The number of CD247 are responsible for proliferation of normal tissues (Ki67 = 0.65 + 0.01, $R^2 = 0.67$, $p < 0.001$). Thus, high CD247 and Ki67 with low CD34 and CD31are rather harmful for sites at the beginning of the range (Figure 4). The better curable sites at the end of the range relate to lack of CD247 and Ki67, but they are naturally abounded with CD34. We classify CD247, as nearest descendants of CD34, because they, as the witnesses, follow to CD34 oppositely, together with Ki67 (Figure 4), manifesting early steps of differentiative activity of CD34. Interesting, that minimal numbers of CD34 (x), *i.e.* bad curability, combines closely with high number of proliferation's marker Ki67 in normal tissues, $y = -0.19\ln(x) + 0.47$, $R^2 = 0.36$, $p = 0.005$ (Figure 4). As it can be logically associating with high number of T cells, the absurd of immune defense against cancer is getting stronger. Hence, bad curability relates to minimum CD34 and maximums CD2, CD247 together with Ki67, and vice versa. Some proves of that are in [20].



Abscissa:CD34 relative units. Ordinate: relative units of CD2 (black circles), CD247 (open circle), and Ki67 (triangles, dotted line).

Figure 4. The content of total T-cells (CD2) marker, young T-cells marker (CD247), and marker of proliferative activity (Ki67) vs. the content of CD34 in normal tissues.

4. Discussion

According [6], the death rate (not the cases) of an American's 2024 decreases along with used numbers (nm.) in the range of malignant tissues sites: 1-lung, 2liver, 3-brain, 4-hematologic, 5-neuro endocrine, 6-renal, 7-pancreas, 8-lymphoid, 9-bladder, 10-colon, 11-lip-oral-head-neck, 12-leukocytic, 13-rectum and anus, 14-thyroid, 15-soft tissue, 16-prostate, 17-skeen, 18-ovarian, 19-breast, 20-uterine, satisfying the equation:

$$y\ (\text{death}) = -17.1 \ln(\text{nm.}) + 63.8,\ R^2 = 0.24,\ p = 0.03 \quad (3)$$

The CD34 in normal tissues increases along this range from lung to the uteri (equation 2). Further discussion will concern of CD34 mostly, as its average value dominates in twenty normal tissues (7.3 r.u.) vs. (0.1 r.u.) for last CD247, and only CD34 inclining makes the tissues more curable. The important role of CD34 in angiogenesis and tumor growth is intensively discussing now [21] [22]. Human pluripotent stem cell' derived the double-positive endothelial progenitors CD34 CD31 is a central link in development of vasculo-genesis, and, consequently, in a tumor growth [23].

The characteristics on **Figure 3** let to conclude, that excess of CD34 and CD31 is protective for CVD and favorite for cancer's curability (prostate, ovary, breast, uteri), in spite of higher number of new cases and deficit of T cells markers (CD2 and CD247) in these sites (**Figure 4**). The opposite combination "lack of CD34 and CD31" with (lung, liver, brain, hematologic) promotes CVD, complicated by atherosclerosis, and bad cancer's curability, in spite of excess of T-cells markers in tissues and lower number of new cases (**Table 2** and **Figure 3** and **Figure 4**). The deficit of "stemness" and "vascularity" in tissues manifests also by increasing of

native Ki67 activity, and vice versa for "excess of CD34 and CD31". The nature of the effects of CD34 on both normal and malignant tissues is unidirectional morphogenesis. It seems, that high native proliferation in tissues exhausts the reserve of "CD34 stemness", which limited at the birth. The local native deficit of morphogenic CD34 markers damps, from one hand, the number of cases, and, on the other hand, weakens of malignant cell's sedentary, shortening the time for early diagnose and nearing the metastasis [24]. **Figure 4** confirms the accelerated proliferation in normal tissues with bad curability of future tumors, and vice versa for tissues, which are more curable. The future tumors according [20] may growth faster too, because the double positive CD34 Ki67endothelium with higher level of Ki67 has the young small vessels compared with mature blood vessels with moderate proliferation by Ki67. For instance, cancers of lung (nb.1)+ colon (nb.10) show prevalence the mortality (M) over incidence (I), as M:I = 1.7 and 1.13, but M:I for cancers of prostate (nb.16) + breast (nb.19) are 0.5 and 0.5. [25]. Our approximation these I:M by corresponding sites is $y = 1.8x - 0.97$, $R^2 = 0.91$, $p = 0.045$. The probability p of calculation in term "two-by-two table" is less, than 0.001. It should be noted, these four sites covered more than 40% of all cancer cases of people both sexes and age 25 - 85+ in the North America, 2022. Thus, high CD34 consumption in normal tissue decline its "stemness", that shortens cancer "homing", nears metastasis, and hinders early diagnosis.

Reproduction of CD34 cells in BM and lymphoid descendance decreases irreversibly by age [10] [26]. Our analysis of data [16] in **Figure 2** showed, that the phenomenon of people +70 years old in entire US population 2020 consists in the replace of a prevalence of cancer death rate by death rate of CVD (**Figure 2, inset**). Ascended part of ratio is $y = 0.49e^{0.011x}$, $R^2 = 0.82$, $p < 0.001$, and descendent part is $y = 320e^{-0.078x}$, $R^2 = 0.9$, $p = 0.05$. The decreasing of the ratio in +70 people arises as result of both the reduction cancer activity and acceleration of deadly atherosclerosis [27]. The dotted lines on **Figure 2** shows, that 50% of carotid plaques and 60% of carotid stenosis belong to the globe people +70 [17]. They achieve maximal predominance of CVD death rate 2024 over cancer from 2, 3-fold at 70 years to 8-fold at 88 years old [16] [27]. Thus, the sharp reversion of a ratio (deaths rates from cancer to CVD' death rate) by age in +70 people (**Figure 2, an inset**) relates to acceleration of deadly atherosclerosis [26] and the age-related deficit of CD34 CD31 "stemness" and "vasculogenity".

It is harmful for cells renewing in vasculo-endothelial system and in the tumor as well. It potentiates predictive potency of "atherosclerotic" HR_{aCVD} from [4], when it applied to test-population 2024 (see the end of 3.2).

Earlier we demonstrate general changing the ratio of malignant to entire nonmalignant pathologies by age in population of US and UK [9] [10]. The lowering both hematopoietic stem cells reproduction and lowering of cancer incidence, mortality and prevalence by advanced age [28] assumes, that the lack of morphogenic support with unidirectional restriction of morphogenesis in both normal and malignant tissues is main base mechanism of aging. Current resource of CD34 cells, in term of

the product their number on the average length of telomeres in bone marrow's lymphoid germ has been decreasing during entire life irreversibly, starting from early adulthood, when body mass positive trajectory reaches study state [10]. This fact implies the morphogenesis as primary function of bone marrow, which fade steadily away in parallel with life shortening after 19 - 21 years old [29]-[31]. That is why, the proliferative resource of BM we consider as a "shagreen leather" of the life during any physiological and pathophysiological conditions [10] [32]. Deficiency of morphogenic hematopoietic stem cells provokes the competition of tissues for them, like that shown on **Figure 2** for cancer and CVD [16].

The limited germinative axis CD133-CD34 is the source of cells, which naturally migrate in organs and used for renewal of both normal and malignant tissues. This complex duality fits the doctrine of morphogenisic, feeding function of CD34 in any tissues, independently of their origin, natural or pathological, including malignant one [8] [33]. Thus, apart from common familiar factors, influenced on malignant pathology at the level of the whole body, like age, gender et cetera, there are wide natural deviation in the feeding of single organs with substances, which originated from BM and are responsible for support of morphogenesis the tissues, independently of its normal or malignant status. This general property is the strong physiological base and challenge for familiar arguments of numerous phenomena of the reciprocal influences among different pathologies, with or without of their treatment.

5. Conclusion

The hazard rate (HR_{CVD}) proposed on the base of cardio-vascular pathology (CVD) for prediction of lowering cancer's incidence in the range: lung, liver, brain, hematologic, neuroendocrine, renal, pancreas, lymphoid, bladder, colon, lip oral head neck, leukocytic, rectum and anus, thyroid, soft tissue, prostate, skin, ovarian, breast, and uterine [4], predicts the cancer's death and mortality (death: cases) instead, being tested by us on estimated cases and death of cancer sites in population of US 2024 [6]. The reason for this inversion of prognostic properties of HR_{CVD} of [4] is quantitative dependence both the level of vascular pathology CVD (y), and future incidence (cases, z) of malignancy in twenty native tissue's sites, mentioned above, from natural content of stem CD34 markers in them (x): $y = 1.4e^{-0.02x}$, $R^2 = 0.2$, $p = 0.05$; $z = 0.0756x + 0.44$, $R^2 = 0.21$, $p = 0.04$. The HR_{CVD} dependence (y) is negative, whereas that for the cases (z) is positive (**Table 1** and **Table 2**). As result, the less of HR_{CVD} (*i.e.* CVD) [4], the more cancer cases (incidence) and CD34 [7] along with the range of tissues ($x = 1 \div 20$) in US 2024 population [6]. The enhancement of stem CD34 marker is accompanied by unidirectional rising of its maturing derivatives, vasculo-endothelial CD31 and total T-cells CD2 marker in sites, which content relate to increasing of future cancer death in this population. As concerns to mortality (death: cases), its decreasing, permanence, or increasing in **Table 2** can be false due to increase of the cases only, changing the both death and cases equally, or prevalence of deaths over cases.

Thus, our investigation discovered only the positive predictive power of **atherosclerotic** CVD, *i.e.* HR_{aCVD} from [4], for number of estimated cancer's death in the twenty sites in US population 2024 [6] (**Table 1**).

In the last century already, the high and different percentage of lymphocytes (up to 65%) were registered in a hundred samples of cancers, extracted by surgery [34]. The physiological diversity of markers of residential cells from bone marrow in the intact tissues of the body reflects this prototype [7]. In oppose to the blood, the average value of CD34 marker in these twenty tissues, being normalized to the corresponding content in bone marrow, prevails over averaged and normalized Tcells marker CD2 more than seven times, that demand the total revision of principles of the onco-immunity created primarily on the investigation of markers in the blood. Dominated stem CD34 markers (y) increases by position (x) in the range of twenty healthy tissues according to linear equation: $y = 0.45x + 2.62$. $R^2 = 0.25$; $p = 0.02$, in parallel with increasing of the number of their CD31 vasculo-endothelial descendants, and future cancer's cases from [6]. Thus, the CD34 "stemness" is more deep cause of two main pathology, because it is a promotor of incidence new cases of cancer, but a protector for CVD (**Table 2**, **Figure 2**, the inset). In oppose to arguments of onco-immunology, the people with age-origin weak "stemness" manifest the more non-malignant pathology, but less cancer's activity.

According this view, cancer's treatment based on killing cells in target tissue is not a good choice, because the sensitive hematopoietic component ("stemness") in it quantitatively prolongs the local tumor's well-being or the long-lasting cancer's "homing", *i.e.* prevents the early metasstases. The poor morphogenisic saturation of tissue by CD34 hinders the wellbeing the normal and malignant cells, nearing the metastasis in case of malignization [10]. Thus, a lowering of "stemness" is unfavorable, because it is complicated by CVD with atherosclerosis and forces the exit of tumor cells into circulation in search of sites with more "stemness". Any hematotoxic therapies, which shortens the *innately limited* resource of morphogenisic CD34, shorten the *life span*, and escalate competition of tissues for regenerative and reparative properties of bone marrow-originated stem migrants. The therapies, which shift the cancer toward "invasiveness", cannot save advanced cancer patients, but will strong complicate their health status. The received arguments focus on unclaimed opportunities for development of cancer therapy guaranteed from "side effects", essence of which is overtreatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Wang, Y., Wang, Y., Han, X., Sun, J., Li, C., Adhikari, B.K., *et al.* (2022) Cardio-Oncology: A Myriad of Relationships between Cardiovascular Disease and Cancer. *Frontiers in Cardiovascular Medicine*, **9**, Article ID: 727487. https://doi.org/10.3389/fcvm.2022.727487

[2] He, D., Qin, K., Li, J., Li, Y., Chen, Z., Xu, J., *et al.* (2024) Increased Incidence Risks

of Cardiovascular Disease among Cancer Patients: Evidence from a Population-Based Cohort Study in China. *International Journal of Cardiology*, **396**, Article ID: 131362. https://doi.org/10.1016/j.ijcard.2023.131362

[3] Bell, C.F. and Leeper, N.J. (2022) Killing the Two Deadly Birds of Atherosclerosis and Cancer with One Stone. *Nature Cardiovascular Research*, **1**, 403-404. https://doi.org/10.1038/s44161-022-00068-y

[4] Bell, C.F., Lei, X., Haas, A., Baylis, R.A., Gao, H., Luo, L., *et al.* (2023) Risk of Cancer after Diagnosis of Cardiovascular Disease. *JACC*: *CardioOncology*, **5**, 431-440. https://doi.org/10.1016/j.jaccao.2023.01.010

[5] Shoutko, A.N. (2022) Tissues Protein Microenvironment and Survival by Age at Cancers. *Acta Scientific Cancer Biology*, **6**, Article No. 7.

[6] Siegel, R.L., Giaquinto, A.N. and Jemal, A. (2024) Cancer Statistics, 2024. *CA*: *A Cancer Journal for Clinicians*, **74**, 12-49. https://doi.org/10.3322/caac.21820

[7] (2021) The Human Protein Atlas. Version 21.

[8] Shoutko, A.N. (2020) Cancer Uses the Common Morphogenesis Source of the Host. *Open Journal of Biophysics*, **10**, 175-190. https://doi.org/10.4236/ojbiphy.2020.104013

[9] Shoutko, A.N. and Ekimova, L.P. (2021) The Lifespan Hormesis Phenomenon in a Population Does Not Make It's Healthier. In: Veeramuthumari, P., Ed., *Challenges in Disease and Health Research*, Vol. 5, Book Publisher International, 79-93. https://doi.org/10.9734/bpi/cdhr/v5/6402d

[10] Shoutko, A.N. (2024) Time for a New Paradigm in Oncology? Viewpoint of the Radiobiologist. *Open Journal of Biophysics*, **14**, 11-55. https://doi.org/10.4236/ojbiphy.2024.141002

[11] Shoutko, A.N. (2023) The Levels of CD34 and CD31 Markers in Normal Organs Determine the Survival Rate in Case of Their Malignization. *Diagnostic Radiology and Radiotherapy*, No. 14, 153-154. (On Russian)

[12] de Araújo, N.D., Gama, F.M., de Souza Barros, M., Ribeiro, T.L.P., Alves, F.S., Xabregas, L.A., *et al.* (2021) Translating Unconventional T Cells and Their Roles in Leukemia Antitumor Immunity. *Journal of Immunology Research*, **2021**, Article ID: 6633824. https://doi.org/10.1155/2021/6633824

[13] Martin, S.S., Aday, A.W., Almarzooq, Z.I., Anderson, C.A.M., Arora, P., Avery, C.L., *et al.* (2024) 2024 Heart Disease and Stroke Statistics: A Report of US and Global Data from the American Heart Association. *Circulation*, **149**, e347-e913. https://doi.org/10.1161/cir.0000000000001209

[14] An, J., Zhang, Y., Zhou, H., Zhou, M., Safford, M.M., Muntner, P., *et al.* (2023) Incidence of Atherosclerotic Cardiovascular Disease in Young Adults at Low Short-Term but High Long-Term Risk. *Journal of the American College of Cardiology*, **81**, 623-632. https://doi.org/10.1016/j.jacc.2022.11.051

[15] Our Changing Population: United States. USA FACTS. https://usafacts.org/data/topics/people-society/population-and-demographics/our-changing-population/

[16] Death Rate from Cardiovascular Diseases by Age Group; Cancer Death Rate by Age Group, United States, 2020. Our World in Data. https://ourworldindata.org/grapher/cardiovascular-disease-death-rate-age-group-who-mdb?time=2020

[17] Song, P., Fang, Z., Wang, H., Cai, Y., Rahimi, K., Zhu, Y., *et al.* (2020) Global and Regional Prevalence, Burden, and Risk Factors for Carotid Atherosclerosis: A

Systematic Review, Meta-Analysis, and Modelling Study. *The Lancet Global Health*, **8**, e721-e729. https://doi.org/10.1016/s2214-109x(20)30117-0

[18] Tanaka, T., Sasaki, N. and Rikitake, Y. (2021) Recent Advances on the Role and Therapeutic Potential of Regulatory T Cells in Atherosclerosis. *Journal of Clinical Medicine*, **10**, Article No. 5907. https://doi.org/10.3390/jcm10245907

[19] Caligiuri, G. (2020) CD31 as a Therapeutic Target in Atherosclerosis. *Circulation Research*, **126**, 1178-1189. https://doi.org/10.1161/circresaha.120.315935

[20] Cimpean, A.M. (2012) Endothelial Cell Activation and Proliferation in Ovarian Tumors: Two Distinct Steps as Potential Markers for Antiangiogenic Therapy Response. *Molecular Medicine Reports*, **5**, 1181-1184. https://doi.org/10.3892/mmr.2012.812

[21] Shimizu, Y. (2022) Mechanism Underlying Vascular Remodeling in Relation to Circulating CD34-Positive Cells among Older Japanese Men. *Scientific Reports*, **12**, Article No. 21823. https://doi.org/10.1038/s41598-022-26089-y

[22] Radu, P., Zurzu, M., Paic, V., Bratucu, M., Garofil, D., Tigora, A., *et al.* (2023) CD34—Structure, Functions and Relationship with Cancer Stem Cells. *Medicina*, **59**, Article No. 938. https://doi.org/10.3390/medicina59050938

[23] Lian, X., Bao, X., Al-Ahmad, A., Liu, J., Wu, Y., Dong, W., *et al.* (2014) Efficient Differentiation of Human Pluripotent Stem Cells to Endothelial Progenitors via Small-Molecule Activation of WNT Signaling. *Stem Cell Reports*, **3**, 804-816. https://doi.org/10.1016/j.stemcr.2014.09.005

[24] Gildea, T.R., DaCosta Byfield, S., Hogarth, D.K., Wilson, D.S. and Quinn, C.C. (2017) A Retrospective Analysis of Delays in the Diagnosis of Lung Cancer and Associated Costs. *ClinicoEconomics and Outcomes Research*, **9**, 261-269. https://doi.org/10.2147/ceor.s132259

[25] Int. Agency for Research on Cancer, World Health Organization (2022) Cancer Today|IARC. https://gco.iarc.who.int

[26] Singh, J. and Singh, A.K. (1979) Age-Related Changes in Human Thymus. *Clinical and Experimental Immunology*, **37**, 507-511.

[27] Age-Adjusted and Age-Specific Atherosclerosis (Coronary Artery Disease) Mortality Rate by Race and Sex. 2023. https://www.mdch.state.mi.us/osr/cri/atherosclerosis.asp

[28] Harding, C., Pompei, F. and Wilson, R. (2011) Peak and Decline in Cancer Incidence, Mortality, and Prevalence at Old Ages. *Cancer*, **118**, 1371-1386. https://doi.org/10.1002/cncr.26376

[29] Nyati, L.H., Pettifor, J.M., Ong, K.K. and Norris, S.A. (2023) The Association between the Timing, Intensity and Magnitude of Adolescent Growth and Body Composition in Early Adulthood. *European Journal of Clinical Nutrition*, **78**, 995-1004. https://doi.org/10.1038/s41430-023-01293-9

[30] Carver, D.E. (2015) Pediatric Red Marrow and Organ Radiation Dose Estimates in Computed Tomography from Monte Carlo Simulations. Ph.D. Dissertation, Vanderbilt University.

[31] Adini, A., Adini, I., Ghosh, K., Benny, O., Pravda, E., Hu, R., *et al.* (2012) The Stem Cell Marker Prominin-1/Cd133 Interacts with Vascular Endothelial Growth Factor and Potentiates Its Action. *Angiogenesis*, **16**, 405-416. https://doi.org/10.1007/s10456-012-9323-8

[32] Shoutko, A.N. (2021) The Possible Involvement of Apoptotic Decay of Terminal Deoxynucleotidyl Transferase-Positive Lymphocytes in the Reutilization of the Extracellular DNA Fragments by Surrounding Living Cells. *Open Journal of Biophysics*, **11**, 371-382. https://doi.org/10.4236/ojbiphy.2021.114014

[33] Shoutko, A.N., Gerasimova, O.A., Fedorov, V.A. and Zherebtsov, F.K. (2019) Non-invasive Vibration-Stress of the Cirrhotic Liver of Patients Waiting for Transplantation Induces of Circulating CD133+ Stem Lymphocytes Committed Phenotypically toward the Liver. *Open Journal of Biophysics*, **9**, 155-168. https://doi.org/10.4236/ojbiphy.2019.93012

[34] Balch, C.M. (1990) Patterns of Human Tumor-Infiltrating Lymphocytes in 120 Human Cancers. *Archives of Surgery*, **125**, 200-205. https://doi.org/10.1001/archsurg.1990.01410140078012