ABSTRACT: Beside genetic and life-style characteristics environmental factors may profoundly influence mortality and life expectancy. The high altitude climate comprises a set of conditions bearing the potential of modifying morbidity and mortality of approximately 400 million people who are permanently residing at elevations above 1500 meters. However, epidemiological data on the effects of high altitude living on mortality from major diseases are inconsistent probably due to differences in ethnicity, behavioral factors and the complex interactions with environmental conditions. The available data indicate that residency at higher altitudes are associated with lower mortality from cardiovascular diseases, stroke and certain types of cancer. In contrast mortality from COPD and probably also from lower respiratory tract infections is rather elevated. It may be argued that moderate altitudes are more protective than high or even very high altitudes. Whereas living at higher elevations may frequently protect from development of diseases, it could adversely affect mortality when diseases progress. Corroborating and expanding these findings would be helpful for optimization of medical care and disease management in the aging residents of higher altitudes.

Key words: High altitude, hypoxia, UV radiation, physical activity, disease, mortality

Beside genetic and life-style characteristics environmental factors may profoundly influence life expectancy [1]. A variety of gene-environment interactions have been demonstrated to have impact on the development of major diseases at advanced ages like cardiovascular and neurodegenerative diseases, diabetes mellitus, and cancer [2, 3]. The high altitude climate comprises a set of conditions bearing the potential of modifying morbidity and mortality of approximately 400 million people who are permanently residing at elevations above 1500 meters [4]. Low barometric pressure and related low partial pressure of oxygen (hypoxia) and increased ultra violet radiation are components of the high altitude climate which are probably interacting in a complex way with genes and other environmental factors [5, 6]. In addition, the outcomes will be influenced by the level of altitude (moderate altitude: 1500 – 2500 m; high altitude: 2500 – 3500 m; very high altitude: > 3500 m), working and housing conditions, behavioral patterns like physical activity, nutrition, smoking and alcohol consumption, and the availability of medical care. It is obvious that some of the altitude-associated conditions may have different impacts on risk factors for developing various diseases and associated mortality or life expectancy. High altitude may have protective effects on cardiovascular diseases and harmful effects on chronic pulmonary disease (COPD) [7] and beneficial effects on mortality from some types of cancer [8]. Mechanisms responsible for these effects are largely unexplored and remain extremely speculative [6, 7, 8]. There are only very few papers evaluating the impact of high altitude living on mortality from major diseases. This, however, would be important to improve preventive medicine in high altitude regions and would probably enhance the general understanding of gene-environmental interactions influencing the development and progression of major...
diseases at advanced ages. Thus, the main goal of the present paper is to present an overview, extracted from the available literature, on the mortality from major diseases when living at higher altitudes.

**Altitude effects on mortality from cardiovascular diseases and stroke**

**Epidemiological data**

Observations from populations of the Andes indicate that both coronary heart disease (CHD) and myocardial infarction are uncommon among residents at high altitude. In a consecutive series of necropsies performed at about 14000 feet (~ 4260 m) there was no case of myocardial infarction or of even moderate coronary artery disease [9]. Large epidemiological studies in the 1970ties confirmed lower mortality from CHD in people residing at higher elevations. Mortimer and colleagues found decreasing mortality rates at altitudes from 914 to over 2135 m in New Mexico [10]. Mortality declined predominantly in males and was 72% at the highest locations compared to the county group below 1220 m. Voors et al. confirmed the negative relationship between altitude and mortality in the highest 99 out of 100 largest cities of the United States up to an altitude of 1650 m [11]. These findings have also been confirmed by more recent studies. In Switzerland the age-standardized mortality rates (per 100,000 person-years) from CHD decreased in men from 289 (95% CI: 275-304) below 300 m of altitude to 242 (193-290) at altitudes above 1500 m and in women from 104 (97-111) < 300 m to 74 (52-97) > 1500 to 1960 m [6]. Mortality rates remained essentially unchanged up to 900 m and then started to decline. The decrease of mortality from stroke was less convincing when compared to that of CHD. After adjustment for age, sex, education, and urbanity the mortality risk for CHD decreased by 22% and that for stroke by 12% per 1000 m increase of altitude [6]. Similar observations have been reported from mortality and population data of the United States (2001 through 2005) for altitudes up to ≥2500 m [7]. However, reduced mortality from CHD in this study was more consistent for women than for men. Again, mortality reduction from stroke was less pronounced and was not statistically significant below 1500 m [7]. Even larger benefits from living in mountainous areas have been reported from Greece [12]. When compared to two lowland villages (Zevgolatio and Aidoniain in the plains of the Peloponnesus region) the hazard ratio for coronary mortality was 0.39 (0.16 to 0.98) for men and 0.46 (0.20 to 1.05) for women living in a mountainous village in rural Greece (Arahova in the Sterea Hellas region, 950 m). Lower mortality from cardiovascular events were also reported for dialysis patients [13] as well as improved survival after heart transplantation [14] in patients living at higher elevation compared to lower ones. There are only very few studies indicating rather detrimental effects of altitude residence on the risk of heart disease which might at least partly be explained by the more extreme conditions of the higher elevations (1500 – 3500 m) where people lived [15]. This is supported by the study of Virue-Ortega et al. demonstrating increasing overall mortality from altitudes between 1500 to 2900m and ≥ 3000 [4]. Of course, differences in ethnicity, behavioral aspects, or medical care between low and high elevations might also contribute to the explanation of the conflicting results. Chronic mountain sickness represents another serious problem arising at higher altitudes (> 3000m) contributing to increased mortality [16].

**How may altitude affect mortality from CHD and stroke?**

**Physical activity and fitness level**

Authors of the early studies, in the 1970ties, suggested increased daily physical activity and the related higher fitness level to be potentially responsible for the observed beneficial effects of living at higher elevations [10] but recent studies do not believe this would be an essential explanation for the differences of life expectancy between populations of low and higher altitudes [6]. However, no study actually ruled out differences in regular physical activity and fitness between these populations. Nowadays it is well established that regular physical activity reduces all traditional risk factors for cardiovascular disease and stroke, i.e. systemic arterial hypertension, elevated low-density and reduced high-density lipoproteins, increased triglyceride levels, insulin resistance and glucose intolerance [17]. At least in the Alps, e.g. in Austria, France, Italy, and Switzerland, higher elevations are typically situated in mountainous areas. They are mostly characterized by a hilly and rugged terrain challenging exercise performance of residents during work and leisure activities [18]. In fact, there are many studies consistently showing a linear dose-response relation between the fitness level and mortality. Kokkinos and colleagues for example demonstrated an approximately 20% lower mortality risk for subjects with an exercise capacity of 5-7 metabolic equivalents (METs; 1 MET = 3.5 mLO2·min⁻¹·kg⁻¹) compared to those achieving below 5 METs [19]. Exercising in the mountains may favour the development of a relatively high fitness level because 5-7 METs are required even for slow uphill walking [18, 20]. If physical activity and fitness are increased at higher altitudes this might well explain part of the lower mortality observed. In contrast, when diseases progress, cardiorespiratory
systems may be rapidly overstrained even during light physical activities, thereby increasing the mortality risk.

**Hypoxia**

The moderate hypoxia stimulus at altitudes up to 2500 m has been suggested as a potential contributor to the beneficial effects on cardiovascular health [7, 21]. From a biological perspective it has been hypothesized that hypoxia inducible factor (HIF) pathways might mediate the reduction of cardiovascular mortality at altitude [13]. HIF-1 is a key regulator of processes such as erythropoiesis, angiogenesis, apoptosis and metabolism [13, 22], which might all have impact on the cardiovascular and cerebrovascular systems. Adaptation effects might partly explain the lower systemic systolic and diastolic blood pressures and lower atherogenic lipoprotein cholesterol (C-LDL) in residents of higher compared to lower regions [23, 24]. High altitude hypoxia could also protect against cardiovascular disease by lowering hepcidin and reticuloendothelial iron storage [25]. Hepcidin has been suggested as a risk factor for atherosclerosis and may be down regulated by HIF which induces erythropoietin and ferroportin [25].

In addition, exercising at altitude may represent a superimposed intermittent hypoxia-like stimulus causing beneficial pre-conditioning effects [26]. It is thought that adaptation to such intermittent hypoxia stimuli which are largely related to nitric oxide production may provide protection against subsequent more severe and prolonged hypoxia as well as protection against other stresses [26, 27]. Effects of this type of intermittent hypoxia include cardioprotection, vasoprotection, neuroprotection, and antistress defense [27]. For example, downhill skiing in alpine regions represents a model of intermittent hypoxia. It has recently been demonstrated that prevalences of hypercholesterolemia, systemic hypertension, diabetes, frequency of mental stress and the occurrence of memory deficits declined in regular downhill skiers with increasing yearly skiing frequency perhaps partially as a consequence of intermittent hypoxia [28]. Adaptation effects to moderate altitudes seem to occur rapidly as it has been shown that the risk of sudden cardiac death decreases steeply after sleeping only one night at higher elevations (> 700 m) [29]. Taken together, it may be the moderate stress imposed by moderate altitude that favours protective adaptations.

**UV-radiation**

Levels of ultraviolet radiation increase by about 10% with every 300 m increase in altitude and may profoundly influence cardiovascular mortality [30]. Protective effects of ultraviolet radiation are mediated by the higher concentrations of Vitamin D, probably by reducing the risk of thrombus formation [31]. Increased cardiovascular and cerebrovascular risk may result from Vitamin D deficiency due to the related increase in parathyroid hormone, which increases insulin resistance and is associated with diabetes, hypertension, and inflammation [32].

**Air pollution**

Decreasing air pollution with increasing altitude may represent another potentially contributing factor to the CHD mortality reduction [6]. The relationship between the exposure to air pollution (short- and long-term) and cardiovascular events has been demonstrated by epidemiological studies. Responsible mechanisms may include enhanced coagulation (thrombosis), acute vasoconstriction, a propensity for arrhythmias, and systemic inflammatory responses promoting progression of atherosclerosis [33].

**Concluding remarks**

Both, behavior patterns and the various environmental conditions of the altitude climate may contribute to the lowering of cardiovascular and cerebrovascular overall mortality which seems to be more distinctive when living at moderate altitudes. However, when diseases progress, living at high altitude may become detrimental.

**Altitude effects on mortality from COPD**

**Epidemiological data**

Male sex, older age, smoking, air pollution and probably also living at higher altitudes are well-known independent risk factors for chronic obstructive pulmonary disease (COPD) [34]. Whether living at higher altitudes is associated with higher or lower prevalences of COPD remains equivocal. Whereas Menezes et al. [35] and Laniado-Laborin et al. [36] found an inverse relationship between altitude and the COPD prevalence, the opposite has been reported by Caballero et al. [34]. Although the regression analysis in the study by Caballero et al. demonstrated a positive association between COPD prevalence and altitude, this association disappears when the city at the highest altitude (Bogota, 2640m) was compared with the city at the lowest altitude (Barranquilla, 18m) [34, 36]. However, there is a broad consensus that mortality from COPD increases with altitude [7, 37]. Cote et al. reported a significant association between COPD and both altitude and smoking [37]. They found that COPD mortality rose by 1/100,000 for each 95m increase of altitude or every 5.4 increase in
mean packs consumed per capita per year. Similar effects have been reported by Ezzati et al. [7]. COPD mortality was 3-4/10,000 greater at altitudes above 1000 m compared to regions within 100m of sea level. In addition, Colorado death records from 1959 to 1976 indicate higher emphysema mortality at these higher elevations when compared with the overall population [38]. There is only one study reporting that mortality was not elevated in COPD patients living at higher altitudes (Mexico City) [39]. The authors hypothesized that this discrepancy might be due to differences in occupational exposures and to the fact that they examined data from a later period when supplemental oxygen use was more prevalent [39]. Taken together existing evidence suggests that long-term residence at high altitude is a potential problem for COPD patients and it seems reasonable that patients suffering from COPD would benefit when migrating to lower altitudes.

**How may altitude affect mortality from COPD?**

Explaining the lower COPD prevalence at higher altitudes, Laniado-Laborin and colleagues suggested that altitude could induce a greater growth of the airways compared with lung size, resulting in an increase of the FEV1/FVC ratio [36]. However, in patients suffering from COPD it has been assumed that even modestly lower ambient oxygen levels from impaired breathing and gas exchange might favour hypoxia and potentiate pulmonary hypertension and the associated development of cor pulmonale [7, 40]. Survival in COPD is adversely affected by pulmonary hypertension depending on the severity of resting mean pulmonary artery pressure [40]. A dose-response relationship between daily hours of oxygen use and survival has been demonstrated. Besides, the presence of chronic mountain sickness may contribute to COPD mortality [41]. Chronic mountain sickness is associated with decreased alveolar ventilation due to a blunted hypoxic ventilatory response leading to low arterial oxygen levels, increased pulmonary hypertension and excessive erythrocytosis [16, 41].

**Concluding remarks**

Based on the available epidemiological data it seems to be conceivable that the COPD prevalence is lower but mortality is higher at altitude. In other words, the risk to suffer from COPD might be reduced when living at higher elevations but when suffering from COPD the mortality risk rises. Thus, COPD patients, especially when disease progresses would benefit from moving down to more oxygen rich sea level regions.

**Altitude effects on mortality from cancer**

**Epidemiological data**

An early study performed in La Paz (Bolivia, ~ 4000m) indicated a higher prevalence for cancer of the cervix, the gallbladder and the thyroid gland in females when compared to other Andean populations [42]. Males have been found to suffer from unusually high rates of testicular cancer [42]. In contrast Amsel et al. reported, based on a 20-year observation period (1950-1969), reduced cancer mortality in high altitude counties [43]. Weinberg et al. (1987) showed that mortality was negatively related to altitude for cancers of the trachea, bronchus, and lung, stomach, small or large intestine, female breast, multiple myeloma, and leukemia considering the time period 1960–1969 [44]. Data from a mountainous region in Spain found a tendency of increased prevalence of melanoma at higher altitudes [45]. Youk et al. demonstrated reduced cancer mortality of people living at altitudes higher than 2134m compared to those living below 305m [8]. Their data are based on mortality and population data of the United States and covered the period from 1950 to 2004. Age-adjusted mortality rates of all cancers, of respiratory system cancers, of non-Hodgkin’s lymphoma, and of breast cancer in women were lower at higher elevations [8]. In a recent paper, Torres et al. demonstrated for the Americans a concentration of mortality from gastric cancer in the mountainous areas along the Pacific Rim, following the geography of the Andes sierra, from Venezuela to Chile, and the Sierra Madre and Cordillera de Centroamérica, from southern Mexico to Costa Rica [46]. However, Torres et al. suggested altitude only to be a surrogate for host genetic, bacterial, dietary, and environmental factors that may cluster in the mountainous regions [46].

**How may altitude affect mortality from cancer?**

In their early study, Amsel et al. speculated that levels of cellular pH at higher altitudes, controlling protein synthesis and mitosis in tumour cells could make cancer cells less likely to grow [43]. Weinberg and colleagues suggested that oxygen produces toxic effects at physiologic levels, and that the effects observed at altitude could reflect an interaction between oxygen levels and background radiation [44]. More likely however, increased Vitamin D levels mediated by the elevated UV radiation at altitude might contribute to the protection against development of cancer. The biologically active form of Vitamin D is recognized to inhibit cell proliferation and to favour differentiation into normally functioning cells [47]. Moreover, Vitamin D has been shown to stabilize chromosomal structure and to protect
against endogenously and exogenously induced chromosomal aberrations [47].

When cancer has developed living at altitude might be less beneficial because HIF-1, stabilized under hypoxic conditions, is known to immortalize tumors by inducing key genes in cancer biology, including angiogenesis, glycolysis, invasion, and metastasis [48].

UV radiation which increases with altitude is the main modifiable risk factor for the development of cutaneous melanoma [45]. Nevertheless, the association between altitude and melanoma prevalence is rather weak which might be partly explained by the protective effects mentioned above. If present, differences in regular physical activity between residents of low and higher elevations may also influence cancer mortality. Strong preventive effects against cancer have been attributed to regular and vigorous physical exercise [49]. Regular exercise has been suggested to reduce cancer incidence up to 40% and these beneficial effects seem to be most pronounced for colorectal and breast cancer [49].

Concluding remarks

Living at higher altitudes may be protective against at least some types of cancer. Again, mortality may be profoundly modified by the complex interactions between behavioral and environmental conditions.

Miscellaneous

Suicide rates seem to be higher at higher altitudes [50]. Betz et al. demonstrated that victims at high and low altitudes differ significantly by multiple demographic, psychiatric, and suicide characteristics. The authors suggest these factors, rather than hypoxia or altitude, to be responsible for the increased suicide rates at high altitude [50]. Based on death certificates from Mexico (1993-1997) the mortality rate for tuberculosis decreased with altitude of residence but was increased for pneumonia and influenza [51]. Whereas beneficial effects on tuberculosis mortality have been attributed to altitude and dryness, altitude related hypoxemia might have negative impact on the outcome of pneumonia and influenza [52]. Finally, children living at high elevations are at special health risk related to hypoxemia during infancy and during acute lower respiratory infections [53].

Conclusions

Interactions between genetic, behavioral and environmental conditions at altitude are complex and may differently impact on mortality from various diseases. Living at higher altitudes seems to be associated with lower mortality from cardiovascular diseases, stroke and certain types of cancer. In contrast mortality from COPD and probably also from lower respiratory tract infections seems to be increased. It may be argued that moderate altitudes are more protective than high or even very high altitudes. Whereas residency at altitude may frequently protect from development of diseases, it could adversely affect mortality when diseases progress. Corroborating and expanding these findings would be helpful for optimization of medical care and disease management in the aging residents of higher altitudes.

References

[1] Finch CE, Tanzi RE (1997). Genetics of aging. Science, 278: 407-411.
[2] Latham KE, Sapienza C, Engel N (2012). The epigenetic lorax: gene-environment interactions in human health. Epigenomics, 4: 383-402.
[3] Joseph PG, Pare G, Anand SS (2013). Exploring gene-environment relationships in cardiovascular disease. Can J Cardiol, 29: 37-45.
[4] Virues-Ortega J, Hogan AM, Baya-Botti A, Kirkham FJ, Baldeweg T, Mahillo-Fernandez I, et al. (2009). Bolivian Children Living at Altitude Project (BoCLA 2006). Survival and mortality in older adults living at high altitude in Bolivia: a preliminary report. Am Geriatr Soc, 57: 1955-1956.
[5] Prabhakar NR, Semenza GL (2012). Adaptive and maladaptive cardiorespiratory responses to continuous and intermittent hypoxia mediated by hypoxia-inducible factors 1 and 2. Physiol Rev, 92: 967-1003.
[6] Faeh D, Gutzwiller F, Bopp M; Swiss National Cohort Study Group (2009). Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland. Circulation, 120: 495-501.
[7] Ezzati M,Horwitz ME, Thomas DS, Friedman AB, Roach R, Clark T, et al. (2012). Altitude, life expectancy and mortality from ischaemic heart disease, stroke, COPD and cancers: national population-based analysis of US counties. J Epidemiol Community Health, 66: e17.
[8] Youk AO, Buchanich JM, Fryzek J, Cunningham M, Marsh GM (2012). An ecological study of cancer mortality rates in high altitude counties of the United States. High Alt Med Biol, 13: 98-104.
[9] Ramos DA, Kruger H, Muro M, Arias-Stella J (1967). Patologia del hombre nativo de las grandes alturas: investigacion de las causas de muerte en 300 autopsias, Bol Of Sanit Panam, 62: 497-501.
[10] Mortimer EA Jr, Monson RR, MacMahon B (1977). Reduction in mortality from coronary heart disease in men residing at high altitude. N Engl J Med, 296: 581-585.
[11] Voors AW, Johnson WD (1979). Altitude and arteriosclerotic heart disease mortality in white residents of 99 of the 100 largest cities in the United States. J Chronic Dis, 32:157-162.
[12] Baibas N, Trichopoulo A, Voridis E, Trichopoulos D (2005). Residence in mountainous compared with...
lowland areas in relation to total and coronary mortality. A study in rural Greece. J Epidemiol Community Health, 59: 274-278.

[13] Winkelmayer WC, Hurley MP, Liu J, Brookhart MA (2012). Altitude and the risk of cardiovascular events in incident US dialysis patients. Nephrol Dial Transplant, 27: 2411-2417.

[14] Wozniak CJ, Baird BC, Stehlik J, Drakos SG, Bull DA, Patel AN, et al. (2012). Improved survival in heart transplant patients living at high altitude. J Thorac Cardiovasc Surg, 143: 735-741.

[15] Al-Huthi MA, Raja'a YA, Al-Noami M, Abdul Rahman AR (2006). Prevalence of coronary risk factors, clinical presentation, and complications in acute coronary syndrome patients living at high vs low altitudes in Yemen. Med Gen Med, 8: 28.

[16] León-Velarde F, Villafuerte FC, Richalet JP (2010). Chronic mountain sickness and the heart. Prog Cardiovasc Dis, 52: 540-549.

[17] Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, et al. (2003). Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease. Circulation, 107: 3109-3116.

[18] Burtscher M (2004). Endurance performance of the elderly mountaineer: requirements, limitations, testing, and training. Wien Klin Wochenschrift, 116: 703-714.

[19] Kokkinos P, Sherrif H, Kheirbek R (2011). Physical inactivity and mortality risk. Cardiol Res Pract, 2011:924945.

[20] Burtscher M (2013). Exercise limitations by the oxygen delivery and utilization systems in aging and disease: coordinated adaptation and deadaptation of the lung-heart muscle axis - a mini-review. Gerontology, 59: 289-296.

[21] Ostadal B, Kolar F (2007). Cardiac adaptation to chronic high-altitude hypoxia: beneficial and adverse effects. Respir Physiol Neurobiol, 158: 224-236.

[22] Shohet RV, Garcia JA (2007). Keeping the engine primed: HIF factors as key regulators of cardiac metabolism and angiogenesis during ischemia. J Mol Med, 85: 1309-1315.

[23] Shrestha S, Shrestha A, Shrestha S, Bhattarai D (2012). Blood pressure in inhabitants of high altitude of Western Nepal. JNMA J Nepal Med Assoc, 52: 154-158.

[24] de Mendoza S, Nucete H, Ineichen E, Salazar E, Zerpa A, Glueck CJ (1979). Lipids and lipoproteins in subjects at 1,000 and 3,500 meter altitudes. Arch Environ Health, 34: 308-311.

[25] Sullivan JL, Bailey DM, Zacharski LR (2010). Letter by Sullivan et al regarding article, "Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland". Circulation, 121: e376.

[26] Cai Z, Luo W, Zhan H, Semenza GL (2013). Hypoxia-inducible factor 1 is required for remote ischemic preconditioning of the heart. Proc Natl Acad Sci U S A, Oct 7, [Epub ahead of print].

[27] Manukhina EB, Downey HF, Mallet RT (2006). Role of nitric oxide in cardiovascular adaptation to intermittent hypoxia. Exp Biol Med (Maywood), 231: 343-365.

[28] Burtscher M, Bodner T, Burtscher J, Ruedl G, Kopp M, Brössner G (2013). Life-style characteristics and cardiovascular risk factors in regular downhill skiers: an observational study. BMC Public Health, 13: 788.

[29] Lo MY, Daniels JD, Levine BD, Burtscher M (2013). Sleeping altitude and sudden cardiac death. Am Heart J, 166: 71-75.

[30] Zittermann A, Gummert JF (2010). Sun, vitamin D, and cardiovascular disease. J Photochem Photobiol B, 101: 124-129.

[31] Scragg R (1981). Seasonality of cardiovascular disease mortality and the possible protective effect of ultra-violet radiation. Int J Epidemiol, 10: 337-341.

[32] Ku YC, Liu ME, Ku CS, Liu TY, Lin SL (2013). Relationship between vitamin D deficiency and cardiovascular disease. World J Cardiol, 5: 337-346.

[33] Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsitt M, et al. Expert Panel on Population and Prevention Science of the American Heart Association (2004). Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation, 109: 2655-2671.

[34] Caballero A, Torres-Duque CA, Jaramillo C, Bolívar F, Sanabria F, Osorio P, et al. (2008). Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude (PREPOCOLD study). Chest, 133: 343-349.

[35] Menezes AMB, Perez-Padilla R, Jardim JRB, Muñoz A, Lopez MV, Valdivia G, et al. (2005). Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet, 366: 1875-1881.

[36] Laniado-Laborin R, Rendón A, Bauerle O (2011). Chronic obstructive pulmonary disease case finding in Mexico in an at-risk population. Int J Tuberc Lung Dis, 15: 818-823.

[37] Cote TR, Stroup DF, Dwyer DM, Horan JM, Peterson DE (1993). Chronic obstructive pulmonary disease mortality: a role for altitude. Chest, 103:1194-1197.

[38] Moore LG, Rohr AL, Maisenbach JK, Reeves JT (1982). Emphysema mortality is increased in Colorado residents at high altitude. Am Rev Respir Dis, 126: 225-228.

[39] Coutsas DB, Samet JM, Wiggins CL (1984). Altitude and mortality from chronic obstructive lung disease in New Mexico. Arch Environ Health, 39:355-359.

[40] Pierson DJ (2000). Pathophysiology and clinical effects of chronic hypoxia. Respir Care, 45: 39-51.

[41] Vearrier D, Greenberg MI (2011). Occupational health of miners at altitude: adverse health effects, toxic exposures, pre-placement screening, acclimatization, and worker surveillance. Clin Toxicol (Phila), 49: 629-640.

[42] Rios-Dalenz J, Correa P, Haenszel W (1081). Morbidity from cancer in La Paz, Bolivia. Int J Cancer, 28: 307-314.

[43] Amsel J, Waterbor JW, Oler J, Rosenwaike I, Marshall K (1982). Relationship of site-specific cancer mortality rates to altitude. Carcinogenesis, 3: 461-465.
Weinberg CR, Brown KG, Hoel DG (1987). Altitude, radiation, and mortality from cancer and heart disease. Radiat Res, 112: 381-390.

Aceituno-Madera P, Buendía-Eisman A, Olmo FJ, Jiménez-Moleón JJ, Serrano-Ortega S (2011). [Melanoma, altitude, and UV-B radiation]. Actas Dermosifiliogr, 102: 199-205.

Torres J, Correa P, Ferreccio C, Hernandez-Suarez G, Herrero R, Cavazza-Porro M, et al. (2013). Gastric cancer incidence and mortality is associated with altitude in the mountainous regions of Pacific Latin America. Cancer Causes Control, 24: 249-256.

Hayes DP (2010). Cancer protection related to solar ultraviolet radiation, altitude and vitamin D. Med Hypotheses, 75(4): 378-382.

Tang CM, Yu J (2013). Hypoxia-inducible factor-1 as a therapeutic target in cancer. J Gastroenterol Hepatol, 28:401-405.

Newton RU, Galvão DA (2008). Exercise in prevention and management of cancer. Curr Treat Options Oncol, 9: 135-146.

Betz ME, Valley MA, Lowenstein SR, Hedegaard H, Thomas D, Stallones L, et al. (2011). Elevated suicide rates at high altitude: sociodemographic and health issues may be to blame. Suicide Life Threat Behav, 4: 562-573.

Pérez-Padilla R, Franco-Marina F (2004). The impact of altitude on mortality from tuberculosis and pneumonia. Int J Tuberc Lung Dis, 8: 1315-1320.

Gardiner CF, Webb GB, Ryder CT (1923). Tuberculosis Mortality in Relation to Altitude. Trans Am Climatol Clin Assoc, 39: 197-208.

Niermeyer S, Andrade Mollinedo P, Huicho L (2008). Child health and living at high altitude. Arch Dis Child, 94: 806-811.