Life history tradeoffs in humans: increased life expectancy with sperm count reduction

Rui-An Wang[1,2] , Ping-Ju Zheng[3], Yi Liu[4], Lei Shang[5]

[1]Shenzhen Key Laboratory of Viral Oncology, The Clinical Innovation & Research Centre, Shenzhen Hospital, Southern Medical University, Shenzhen, Guangdong Pr. 518100, China.[2] Department of Pathology, Shenzhen Hospital, Southern Medical University, Shenzhen, Guangdong Pr. 518100, China, [3]Department of Oncology, Shenzhen Hospital, Southern Medical University, Shenzhen, Guangdong Pr. 518100, China, [4]Medical College, Xi'an Peihua University, Xi'an, Shaanxi Pr. 710125, China,[5]Department of Health Statistics, The Fourth Military Medical University, Xi'an, Shaanxi Pr. 710032, China

TABLE OF CONTENTS

1. ABSTRACT

Although not without controversy, as a general trend, the human sperm count is declining world-wide. One major reason for such a decline is an increase in the human life-span. According to the life history tradeoff theory, fecundity is inversely related to the lifespan; the longer the lifespan, the lower the fecundity. This is essential to the maintainance of diversity and balance of different species. Such a corrleation validated by experimental data that show that the extension of life in *Caenorhabditis elegans*, *Drosophila* and *Rodents* is associated with reduction in fecundity. The demographic data from a public data source, shows that the total fertility rate is positively correlated with the infant death rate, it is inversely correlated with the life expectancy. We postulate that the fall in spermatogenesis might be regulated by the neuroendocrine system that underlie human longevity.

2. THE LIFE HISTORY TRADEOFF EVOLUTION THEORY AND THE PRINCIPLE OF BIORELATIVITY

Darwinian evolution progresses in only one direction. This begs the question, if everything moves forward, how are species diversity and balance maintained in the biosphere? Therefore, there must be other rules, which help regulate this delicate balance. The fecundity of any organism appears to be influenced by three factors: lifespan, body size, and position on the food chain. Generally speaking: the longer the lifespan, the lower the fecundity; the larger the body size, the lower the fecundity; the higher the position in the food chain, the lower the fecundity (1). Similarly, the life history trade-off theory of ecology deems that there are trade-offs between the genetic traits of organisms (2).

Of the three rules in this restriction dogma, the restriction of lifespan on fecundity is extremely important in the biomedical sciences. The phenomenon of an inverse relationship between lifespan and fecundity was first described in the 1960s (3), and is universal in many species including mammals and birds (4, 5). We designated this phenomenon the "biorelativity" principle (6). Based on this rule, we can conclude that the "Darwinian demon" (7), a hypothetical creature with infinite lifespan and infinite fecundity, is irrational.

We will elaborate upon the influence of the lifespan on fecundity with examples including microorganisms, cells of multicellular organisms, and plants, as well as humans.

If we compare the growth rate of bacteria, we see that the generation time of *Esherichia coli* is about 18-20 minutes, while the generation time of *Mycobaacterium tuberculosis* is over 18 hours, and the generation time of *Mycobaacterium leprosy* is unknown since it has never been successively cultivated *in vitro*. It is currently unclear why *E. coli* and most common bacteria rapidly reproduce and why the mycobacteria causing tuberculosis and leprosy reproduce so slowly. However, it is surprisingly simple if we take the lifespan of the different germs into account. Mycobacteria have a long lifespan, possess strong endurance to harsh environments, and thus do not need high fecundity for their existence in the biosphere. Conversely, *E. coli* and most other bacteria have a short lifespan, so they must have high fecundity for their continued existence. Therefore, short-living unicellular organisms would expand their population much faster than their long-living peers (6, 8).

Yeast is a good model of lifespan and senescence research. It gives rise to progenies by asymmetric division, i.e., sporulation. Yeast has two types of lifespan (9). One is a chronological lifespan, which is the time that individual yeast survives. The other is termed replicative lifespan, which is the number of daughter cells produced by the mother cell (9). By definition we know that the replicative lifespan is an indication of the fecundity of yeast. Sir2, an extensively studied gene, which is involved in the regulation of the lifespan of many classes of organisms, has opposite effects on the chronological and replicative lifespan of the yeast (10).

The restriction of lifespan on the growth rate in unicellular mechanisms is not unique to bacteria. Interestingly, this rule is also applicable to the cultured normal and cancer cells. When the anti-apoptotic protein Bcl-2 is ectopically overexpressed, both the apoptosis and cell growth rate decline (11). Conversely, proteins that promote cell death, such as the cell death receptor CD95 (12) and the apoptosis executor protein caspase-3, all promote cell growth in both *in vitro* and *in vivo* experiments (13). Although many researchers assume that cancer cells are "apoptosis resistant" (14), these malignant cells are de facto "short living cells", as proved by Alexis Carrel 90 years ago (15). We suggest that increased apoptosis and necrosis stimulate the growth and metastasis of cancer, and thus are the root cause of malignancy (16, 17).

Biorelativity also applies to the plant kingdom. If we compare the growth rate of three different kinds of *ginseng*, we see that the wild ginseng grows at a much slower rate than the Chinese or Korean garden ginseng and American ginseng, which are all farm grown. The simple reason is that the wild ginseng can live up to hundreds of years, while most garden ginseng only live for a few years. Hence, wild ginseng is extremely rare and highly valuable.

With regard to humans, it is a well-established fact that fertility rates are high in poor countries or regions (Figure 1) (18). However, the fertility rate is not in a linear relationship with GDP per capita, but rather in an antilog relationship. This type of curve means that the fertility rate is not directly related to GDP *per se*, but rather indirectly related to GDP. In poor countries life expectancy is usually
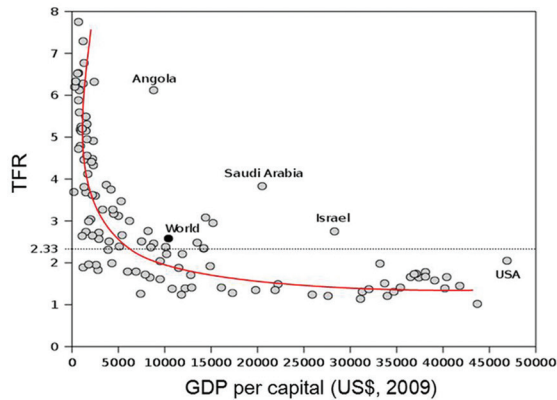
Figure 1. Relationship between gross domestic product (GDP) per capita and total fertility rate (TFR). TFR drops rapidly as the GDP increases until GDP reaches $8 000 per capita. After that point, TFR remains relatively constant, regardless of GDP per capita. Data source: CIA World Fact Book, 2009. Figure was adopted from Wikipedia. http:// en. wikipedia. org/ wiki/total_fertility_rate.
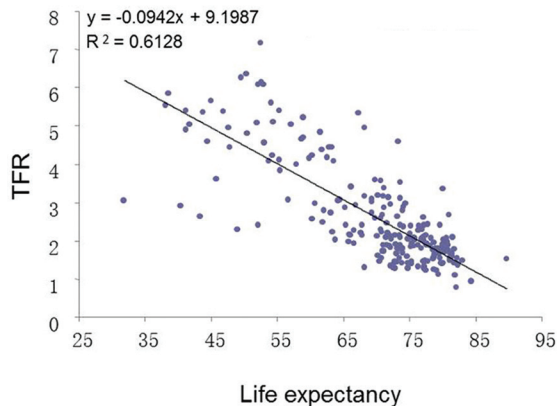
Figure 2. Relationship between life expectancy and total fertility rate (TFR). TFR decreases as as the life expectancy increases. $P < 0.0001$. Original data source: CIA World Fact Book, 2012.

Table 1. Restriction of total fertility rate (TFR) by life expectancy

Life expectancy	TFR
65	3.08
70	2.61
75	2.14
80	1.66
85	1.10
90	0.72
TFR was calculated by the formula in Figure 2, y = -0.0942x+9.1987	

shorter than in developed countries; therefore it is possible that life expectancy may influence the fertility rate. Based on a correlation analysis of demographic data from 222 countries and regions from the CIA World Fact Books[19], the total fertility rate (TFR) which is the average number of times a woman gives birth in her whole life, is negatively correlated with life expectancy (Figure 2). It can be seen that with the extended life expectancy, the TFR declines (Figure 2 and Table 1). The question remaining now is whether the fecundity of human beings also declines with the extension of their life expectancy?

3. IT IS A FACT THAT THE HUMAN SPERM COUNT IS DECLINING

Since Carlsen *et al* [20] first reported that the human sperm count had declined by 50% in 1992 compared with 50 years prior [20], many research reports have confirmed, that in general, human sperm count is declining [21, 22]. These reports covered a wide range of geographical regions including several countries in Europe [23, 24], North Africa [25, 26] , North America [21], Oceania [27], and Asian countries such as India[28] and China [29]. Yet there are also studies which reported no changes [30, 31], and thus called into question the reliability of those reports supporting a reduced sperm count [30-36]. In an organized cohort study of around 5,000 young Danish participants, lasting up to 15 years, there was no evidence of a reduction in sperm count [35]. However, the counts averaged just 40-50 million per mL [35].

Now the question is how to reconcile the different findings. As Joefe highlighted, we could not assume that the sperm count reduction was occurring uniformly worldwide [37]. It is highly possible that in some places it had occurred earlier and had already stabilized in the tested time period. A meta-analysis showed that from the mid-1940s to 1996, the sperm counts dropped from 170 to 60 million per mL in Europe, but in North America, the sperm counts dropped from 110 to 60 million

per mL between the early 1930s and 1996 (21). Therefore, it is not hard to understand that in a 10-year period, some countries/regions may not experience much change, such as Sweden (38) and Korea (31). Furthermore, with regard to young Danish men, the already low sperm count level will probably remain stable for many years.

4. HOWEVER, THE CAUSES OF SPERM COUNTS REDUCTION ARE EXTREMELY ILLUSIVE

If we accept human sperm count reduction as a fact, then the important question is what caused this decline in human sperm count? Environmental factors, including air pollution, water pollution, food contamination by pesticides, endocrine disruptors, and transgenic crops, are most commonly cited as being responsible for the decline in sperm count. Other factors such as lifestyle changes have also been suggested as being responsible. Nowadays, we lead a more sedentary lifestyle and are less physically active than before: we watch more television, and spend more time on computers, cellular phones and computer games.

4.1. Environmental pollutions

People are well aware about environmental pollution. When asked about what types of harm pollution causes, people will mostly name sperm count reduction and cancer. Although, it is well established that pollution has harmful effects on health, the link between pollution and a reduction in sperm count has not been definitively proven.

If pollution is the culprit of sperm count reduction, then the scale of the decline should be proportional to the severity of pollution. When the pollution is corrected, the sperm count should recover in due course. However, we observed the most severe sperm count decline in countries with better environmental conservation policies such as in Denmark and France. By comparison, the environment in China and India is much poorer, yet these countries have a higher sperm count than that of Denmark and France.

In the years around 2005, the average sperm count in China and India was around 65-70 million per mL (29, 39), while it is 45-50 million per mL in Denmark and France (24, 35).

Taking a historical perspective, we know that in the 1950s, London was badly polluted, but the environment had improved by the 1990s and is much better today. Yet a corresponding increase in the sperm count of British men was not observed.

Some people may argue that it may not be due to general pollution but rather some specific chemical components such as BPA, DBP, and dioxin, the so-called endocrine disruptors. However, all the studies with BPA have failed to prove a link between BPA and sperm count reduction (40). Indeed, there were studies which showed reproductive toxicity to spermatogenesis of some agents which could be found in environmental pollutants (41). But the problem is that animal experiments do not accurately reflect the real world, as the animals in the experiments were exposed to dosages up to several thousand times that found in the real world. Surely we cannot infer the results from such studies and conclude that environmental factors are the major cause of sperm count reduction. In fact, these toxicological studies failed to yield anything useful outside of their tested dosage range.

One logical question is that if the environmental factors contributed to human sperm count reduction, then what about the sperm count in animals? Interestingly, available data from 1936 to the 1990s showed no difference in the sperm counts of bulls, boars, rams, and stallions (42, 43). This data allows us to compare the human sperm count data between 1936 and now. Taken together, this evidence is enough to dismiss environmental pollution as a possible cause for human sperm count reduction, unless proven otherwise.

The facts that negate the notion of environmental pollution as the cause of sperm count decline are summarized in Table 2.

Table 2. Facts that indicate that environmental pollution is not the cause of declining sperm counts

1. If pollution is the cause of the decline in sperm count, then the reduction of sperm counts should be parallel to the degree of pollution. Obviously this is not the case. Environmental pollution has long been a significant problem in China but the sperm count in China is much higher than in Western Europe (20, 39-42), where environmental preservation is much better.
2. If pollution is the cause, when pollution declines, the sperm counts should return to their previous levels. Nevertheless, in UK, despite occurrence of environmental improvements since the 1950s, there were no reports of sperm count increase over this period.
3. If the pollution of air, water or by transgenic food accounts for the sperm count decline, then animal sperm count should show a similar degree of reduction. The fact is, there has been no change in the sperm counts of boar, horse, cattle and goat compared with that of 1930s (37, 38).

4.2. Lifestyle changes

Lifestyle changes, such as less physical exercise, use of computers and cellular phones may also be an alternative explanation for decreased sperm count (44). However, there is no solid evidence for any of these claims, and they remain simply untested hypotheses (45). The existence of such suspects is because we cannot explain the sperm count reduction with environmental pollution, and so far we have not nailed down any specific cause that can reliably explain this issue.

However, the increase in meat consumption might play a causative role in sperm count reduction (46). The reason is as mentioned earlier: the restriction of fecundity by the position in the food chain.

4.3. Extended lifespan as the cause of sperm count reduction

There is a saying that the bigger picture is lost when focusing only on a specific spot. We have been trying to determine a specific agent or a signaling pathway that is responsible for the reduction in sperm count. As yet we have no proof that this specific agent or the signaling pathway really exists.

Therefore, let us take on a holistic perspective. As we discussed earlier, no organism exists with a long lifespan and high fecundity. When the average lifespan is extended, the fecundity must decline. Otherwise, the balance between the species cannot be maintained. We put this relationship into a formula, that is,

$$X*Y=C$$

Here variate X stands for lifespan, variate Y stands for fecundity, and C is an elastic constant value. To keep the C relatively stable, when X is increased, Y will come down. When $X \rightarrow \infty$, then $Y \rightarrow 0$.

Laboratory experiments have repeatedly supported this principle. As aforementioned in the cultured cells, when the anti-apoptotic protein Bcl-2 was overexpressed and when apoptosis was inhibited then cell growth was inhibited (11). A similar story is also found with p202, an interferon-induced protein, which is capable of inhibiting both apoptosis and cell growth in fibroblasts and prostate cancer cells (47-50). Conversely, when c-myc, the oncogene that drives mitosis is overexpressed, many cells die (51). Apoptosis promoting proteins usually promote the growth of normal and cancer cells. For example, CD95, Bax, and JNKs all promote cancer cell growth (12, 52, 53). Caspase-3, the final executioner protein in the apoptosis pathway, is also critical for the normal and cancer cell growth (13). Based on this, it is not hard to understand that infant death is a stimulator of the human fertility rate (Figure 3). Actually, if the infant death rate is high, life expectancy will be low because the calculation takes all deaths into account. So when the stimulation from infant death declines, the need and desire of giving birth will be low.

Experiments in metazoans also showed similar results. In *Caenorhabditis elegans*, *drosophila* and rodents, diet restriction
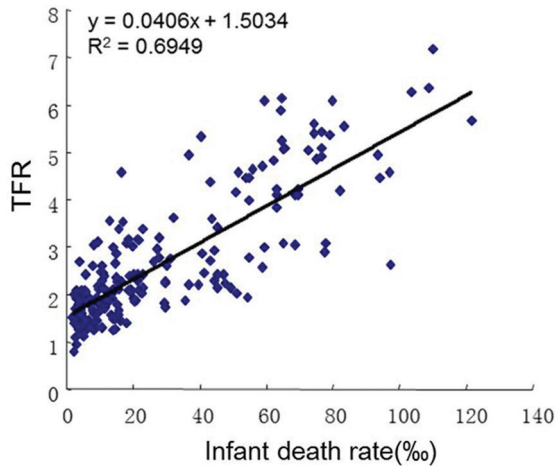
Figure 3. Relationship between infant death rate and total fertility rate (TFR). TFR increases as infant death rate increases, suggesting that child mortality is a strong stimulator of child birth. P<0.0001. Original data source: CIA World Fact Book, 2012.

extended their lifespan, but also invariably reduced their fecundity. That is well known as a life-for-fecundity tradeoff (3). Conversely, when a genetic locus CG11700 in *drosophila* was mutated, the fecundity of the male fly was increased but their lifespan shortened (54). The experimental evidence that supports prolonged lifespan as the cause of human sperm count decline is summarized in Table 3.

If we put together all the evidence, as summarized in Table 3 and 4, we may well conclude that the increased life expectancy is the most probable cause for the reduction of human sperm count. This explains why the sperm count between the mid-1940s and 1996 in Europe dipped from 170 to 60 million per mL, and from 110 to 60 million per mL in North America between the early 1930s and 1996 (21). The reason for the high sperm count during the mid-1940s in Europe was probably due to stimulation from World War II.

To date, scientists have not elucidated the mechanism of this inverse relationship, even in lower organisms such as *drosophila* and *C. elegans*. However, a tentative explanation could be that when the human life expectancy was extended, the need and desire for giving birth was reduced; since spermatogenesis is a neuroendocrine-regulated process, sperm counts fell as life span increased. A more vague explanation from the life history tradeoff theory is that with the extension of the lifespan, there are less energy and efforts allocated to the fecundity (2). Based on our proposed explanation, we predict several consequences. First of all, human sperm count will not be decreasing forever, but rather will reach a stable level as the life expectancy of human beings cannot be extended limitlessly. This has already been proven by some studies such as those in Korea (31) and Sweden (30). If finally life expectancy stabilizes at around 85 years of age, the sperm count could stabilize between 40-50 million per mL, and that will be more than enough to maintain the reproductive ability. Secondly, not all the regions in the world are currrently facing the problem of sperm count reduction. Countries with political instability, war, and other problems which seriously lower the life expectancy and thus have a high TFR are expected to have higher sperm counts than the countries with long life expectancy and lower TFR. Namely, Asian countries such as Iraq, Afghanistan, Yemen and certain countries in central and southern regions of Africa are not expected to have sperm count reduction. Thirdly, regions hit by disasters such as earthquakes may stimulate an increase in birth rate, and thus may experience a rebound in sperm count for a period of time.

5. CODA

Evidence indicates that the reduction of human sperm count does not happen in every corner of the world at the same time and same pace. As long as life expectancy increases, the trend will not stop. Environmental pollution does not have much to do with the sperm count reduction since it does not contribute towards an increase in life expectancy. In fact, Herbert Spencer foretold that the reproductive ability of human beings would decrease with the increase in their competitiveness approximately 150 years ago. However, there is a bottom for the average human sperm count since the life expectancy has its upper limits. Indeed, both

Table 3. Experimental evidence which supports that extension of lifespan reduces fecundity

1. Single cells---cultured mammalian cells. When anti-apoptotic proteins were ectopically overexpressed, cell growth was inhibited (11, 47-50).
2. Single cells---yeast. Lack of Sir2, along with calorie restriction or other mutations was found to dramatically extend the chronological lifespan of yeast but reduce the replicative lifespan/fecundity. Conversely, overexpression of Sir2 increased the replicative lifespan but shortened longevity of the yeast (10).
3. *Caenorhabditis elegans* and drosophila. By dietary restriction and genetic manipulations, the longevity of the lifespan of *C. elegans* and *drosophila* can be extended. As a trade-off, the fertility rate declines (43, 55).
4. Animals-mouse. Mice also showed similar results to that of *C. elegans* and *drosophila*. Dietary restriction, and a variety of genetic manipulations or spontaneous mutations extended the lifespan but invariably reduced the fecundity of mice (56-58).

Table 4. Facts that support extension of life expectancy as the major course of sperm count decline

1. Sperm count declines more in countries where life expectancy is higher (24, 29, 59).
2. As the life expectancy reaches a plateau, the sperm count is also stabilized, as seen in Denmark (35).
3. Large scale population reduction which reduced life expectancy, such as the Second World War, increased the sperm count. In Europe, the sperm count was 170 million per mL in the 1940s, a value 50% higher than that recorded in in North America in the 1930s, (110 million per mL) (21).
4. Life threatening situation like war produced baby boom, as reported in Ukraine (60).

the life expectancy and the sperm count have not changed much in developed countries such as Denmark in recent years. As such, it appears that there is little that can be done about the current decline in human sperm count since it is unlikely that we would sacrifice our lifespan.

6. ACKNOWLEDGEMENTS

7. REFERENCES

1. R. A. Wang: The fecundity restriction dogma and the irrationality of current cancer theory. *Medicine and Philosphy (Chinese)*, 33(12B), 44-46 (2012)

2. D. Fabian and T. Flatt: Life history evolution. *Nature Education Knowledge*, 3(10), 24 (2012)

3. G. Willams: Natural selection, the cost of reproduction, and a refinement of Lack's principle. *Amer Natur*, 100, 687-690 (1966)
DOI: 10.1086/282461

4. D. J. Holmes, R. Fluckiger and S. N. Austad: Comparative biology of aging in birds: an update. *Exp Gerontol*, 36(4-6), 869-83 (2001)
DOI: 10.1016/S0531-5565(00)00247-3

5. A. Read and H. PH: Life history differences among the eutherian radiations. *J Zool*, 219, 329-353 (1989)
DOI: 10.1111/j.1469-7998.1989.tb02584.x

6. R. A. Wang, Z. Y. Ke, Y. Liang, T. Yang, J. H. Qin and L. Wang: Why is mycobacterium tuberculosis hard to grow? the principle of biorelativity explains. *J Clin Exp Pathol*, 4(3), 176 (2014)
DOI: 10.4172/2161-0681.1000176

7. R. Law: Optimal life histories under age-specific predation. *Am Nat*, 114, 399-417 (1979)
    DOI: 10.1086/283488

8. R.A. Wang: Life history tradeoffs of pathogens and the treatment principle of antibiogenesis. *Genes & Diseases*, 4, 154-158 (2017)
    DOI: 10.1016/j.gendis.2017.07.004

9. S. M. Jazwinski: Yeast replicative life span--the mitochondrial connection. *FEMS Yeast Res*, 5(2), 119-25 (2004)
    DOI: 10.1016/j.femsyr.2004.04.005

10. P. Fabrizio, C. Gattazzo, L. Battistella, M. Wei, C. Cheng, K. McGrew and V. D. Longo: Sir2 blocks extreme life-span extension. *Cell*, 123(4), 655-67 (2005)
    DOI: 10.1016/j.cell.2005.08.042

11. K. Knowlton, M. Mancini, S. Creason, C. Morales, D. Hockenbery and B. O. Anderson: Bcl-2 slows *in vitro* breast cancer growth despite its antiapoptotic effect. *J Surg Res*, 76(1), 22-6 (1998)
    DOI: 10.1006/jsre.1998.5277

12. L. Chen, S. M. Park, A. V. Tumanov, A. Hau, K. Sawada, C. Feig, J. R. Turner, Y. X. Fu, I. L. Romero, E. Lengyel and M. E. Peter: CD95 promotes tumour growth. *Nature*, 465(7297), 492-6 (2010)
    DOI: 10.1038/nature09075

13. Q. Huang, F. Li, X. Liu, W. Li, W. Shi, F. F. Liu, B. O'Sullivan, Z. He, Y. Peng, A. C. Tan, L. Zhou, J. Shen, G. Han, X. J. Wang, J. Thorburn, A. Thorburn, A. Jimeno, D. Raben, J. S. Bedford and C. Y. Li: Caspase 3-mediated stimulation of tumor cell repopulation during cancer radiotherapy. *Nat Med*, 17(7), 860-6 (2011)
    DOI: 10.1038/nm.2385

14. D. Hanahan and R. A. Weinberg: Hallmarks of cancer: the next generation. *Cell*, 144(5), 646-74 (2011)
    DOI: 10.1016/j.cell.2011.02.013

15. A. Carrel: Mechanism of formation and growth of malignant tumors. *Ann Surg*, LXXXII(1), 1-13 (1925)

    DOI: 10.1097/00000658-192507010-00001

16. R. A. Wang, Q. L. Li, Z. S. Li, P. J. Zheng, H. Z. Zhang, X. F. Huang, S. M. Chi, A. G. Yang and R. Cui: Apoptosis drives cancer cells proliferate and metastasize. *J Cell Mol Med*, 17(1), 205-11 (2013)
    DOI: 10.1111/j.1582-4934.2012.01663.x

17. R. A. Wang, Z. S. Li, Q. G. Yan, X. W. Bian, Y. Q. Ding, Du X, B. C. Sun, Y. T. Sun and X. H. Zhang: Resistance to apoptosis should not be taken as a hallmark of cancer. *Chin J Cancer*, 33(2), 47-50 (2014)
    DOI: 10.5732/cjc.013.10131

18. http:// en. wikipedia. org/ wiki/ total_fertility_rate.

19. https://www.cia.gov/library/publications/ the-world-factbook/. Data extracted on 2012-10-10.

20. E. Carlsen, A. Giwercman, N. Keiding and N. E. Skakkebaek: Evidence for decreasing quality of semen during past 50 years. *BMJ*, 305(6854), 609-13 (1992)
    DOI: 10.1136/bmj.305.6854.609

21. S. H. Swan, E. P. Elkin and L. Fenster: The question of declining sperm density revisited: an analysis of 101 studies published 1934-1996. *Environ Health Perspect*, 108(10), 961-6 (2000)
    DOI: 10.1289/ehp.00108961

22. P. Sengupta, S. Dutta and E. Krajewska-Kulak: The Disappearing Sperms: Analysis of Reports Published Between 1980 and 2015. *Am J Mens Health*, 11(4), 1279-1304 (2017)
    DOI: 10.1177/1557988316643383

23. E. Carlsen, A. Giwercman and N. E. Skakkebaek: Declining sperm counts and increasing incidence of testicular cancer and other gonadal disorders: is there a connection? *Ir Med J*, 86(3), 85-6 (1993)

24. M. Rolland, J. Le Moal, V. Wagner, D. Royere and J. De Mouzon: Decline in semen concentration and morphology in a sample of 26,609 men close to general population between 1989 and 2005 in

France. *Hum. Reprod.*, 28(2), 462-70 (2013)
DOI: 10.1093/humrep/des415

25. N. C. Feki, N. Abid, A. Rebai, A. Sellami, B. B. Ayed, M. Guermazi, A. Bahloul, T. Rebai and L. K. Ammar: Semen quality decline among men in infertile relationships: experience over 12 years in the South of Tunisia. *J Androl*, 30(5), 541-7 (2009)
DOI: 10.2164/jandrol.108.005959

26. P. Sengupta, U. Nwagha, S. Dutta, E. Krajewska-Kulak and E. Izuka: Evidence for decreasing sperm count in African population from 1965 to 2015. *Afr Health Sci*, 17(2), 418-427 (2017)
DOI: 10.4314/ahs.v17i2.16

27. R. Shine, J. Peek and M. Birdsall: Declining sperm quality in New Zealand over 20 years. *N Z Med J*, 121(1287), 50-6 (2008)

28. A. Sk, J. V, K. G, U. D and K. P: Declining semen quality among south Indian infertile men: A retrospective study. *J Hum Reprod Sci*, 1(1), 15-8 (2008)
DOI: 10.4103/0974-1208.38972

29. C. Huang, C. Yao, C. Wang, J. Jiang and G. Chen: Changes of semen quality in Chinese fertile men from 1985 to 2008. *Chin J Androl* (8), 684-688 (2010)

30. S. Berling and P. Wolner-Hanssen: No evidence of deteriorating semen quality among men in infertile relationships during the last decade: a study of males from Southern Sweden. *Hum Reprod*, 12(5), 1002-5 (1997)
DOI: 10.1093/humrep/12.5.1002

31. J. T. Seo, K. H. Rha, Y. S. Park and M. S. Lee: Semen quality over a 10-year period in 22,249 men in Korea. *Int J Androl*, 23(4), 194-8 (2000)
DOI: 10.1046/j.1365-2605.2000.00226.x

32. P. Bromwich, J. Cohen, I. Stewart and A. Walker: Decline in sperm counts: an artefact of changed reference range of "normal"? *BMJ*, 309(6946), 19-22 (1994)

DOI: 10.1136/bmj.309.6946.19

33. J. P. Bonde, C. H. Ramlau-Hansen and J. Olsen: Trends in sperm counts: the saga continues. *Epidemiology*, 22(5), 617-9 (2011)
DOI: 10.1097/EDE.0b013e318223442c

34. A. Benshushan, O. Shoshani, O. Paltiel, J. G. Schenker and A. Lewin: Is there really a decrease in sperm parameters among healthy young men? A survey of sperm donations during 15 years. *J Assist Reprod Genet*, 14(6), 347-53 (1997)
DOI: 10.1007/BF02765840

35. V. E. Te and J. P. Bonde: Misconceptions about falling sperm counts and fertility in Europe. *Asian J. Androl.*, 15(2), 195-8 (2013)
DOI: 10.1038/aja.2012.122

36. A. J. Wilcox: On sperm counts and data responsibility. *Epidemiology*, 22(5), 615-6 (2011)
DOI: 10.1097/EDE.0b013e318225036d

37. M. Joffe: What has happened to human fertility? *Hum. Reprod.*, 25(2), 295-307 (2010)
DOI: 10.1093/humrep/dep390

38. J. Axelsson, L. Rylander, A. Rignell-Hydbom and A. Giwercman: No secular trend over the last decade in sperm counts among Swedish men from the general population. *Hum Reprod*, 26(5), 1012-6 (2011)
DOI: 10.1093/humrep/der045

39. P. C. Pal, M. Rajalakshmi, M. Manocha, R. S. Sharma, S. Mittal and D. N. Rao: Semen quality and sperm functional parameters in fertile Indian men. *Andrologia*, 38(1), 20-5 (2006)
DOI: 10.1111/j.1439-0272.2006.00685.x

40. R. M. Sharpe: Is it time to end concerns over the estrogenic effects of bisphenol A? *Toxicol. Sci.*, 114(1), 1-4 (2010)
DOI: 10.1093/toxsci/kfp299

41. M. Joffe: Infertility and environmental pollutants. *Br Med Bull*, 68, 47-70 (2003)
DOI: 10.1093/bmb/ldg025

42. B. P. Setchell: Sperm counts in semen of farm animals 1932-1995. *Int J Androl*, 20(4), 209-14 (1997)
DOI: 10.1046/j.1365-2605.1997.00054.x

43. J. L. van Os, M. J. de Vries, N. H. den Daas and L. L. Kaal: Long-term trends in sperm counts of dairy bulls. *J Androl*, 18(6), 725-31 (1997)

44. S. La Vignera, R. A. Condorelli, E. Vicari, R. D'Agata and A. E. Calogero: Effects of the exposure to mobile phones on male reproduction: a review of the literature. *J Androl*, 33(3), 350-6 (2012)
DOI: 10.2164/jandrol.111.014373

45. Z. O. Merhi: Challenging cell phone impact on reproduction: a review. *J Assist Reprod Genet*, 29(4), 293-7 (2012)
DOI: 10.1007/s10815-012-9722-1

46. T. K. Jensen, B. L. Heitmann, M. B. Jensen, T. I. Halldorsson, A. M. Andersson, N. E. Skakkebaek, U. N. Joensen, M. P. Lauritsen, P. Christiansen, C. Dalgard, T. H. Lassen and N. Jorgensen: High dietary intake of saturated fat is associated with reduced semen quality among 701 young Danish men from the general population. *Am J Clin Nutr*, 97(2), 411-8 (2013)
DOI: 10.3945/ajcn.112.042432

47. D. Choubey: P202: an interferon-inducible negative regulator of cell growth. *J Biol Regul Homeost Agents*, 14(3), 187-92 (2000)

48. D. H. Yan, A. Abramian, Z. Li, Y. Ding, Y. Wen, T. J. Liu and K. Hunt: P202, an interferon-inducible protein, inhibits E2F1-mediated apoptosis in prostate cancer cells. *Biochem Biophys Res Commun*, 303(1), 219-22 (2003)
DOI: 10.1016/S0006-291X(03)00320-6

49. D. Koul, R. Lapushin, H. J. Xu, G. B. Mills, J. U. Gutterman and D. Choubey: p202 prevents apoptosis in murine AKR-2B fibroblasts. *Biochem Biophys Res Commun*, 247(2), 379-82 (1998)
DOI: 10.1006/bbrc.1998.8804

50. D. H. Yan, Y. Wen, B. Spohn, D. Choubey, J. U. Gutterman and M. C. Hung: Reduced growth rate and transformation phenotype of the prostate cancer cells by an interferon-inducible protein, p202. *Oncogene*, 18(3), 807-11 (1999)
DOI: 10.1038/sj.onc.1202369

51. Y. Shi, J. M. Glynn, L. J. Guilbert, T. G. Cotter, R. P. Bissonnette and D. R. Green: Role for c-myc in activation-induced apoptotic cell death in T cell hybridomas. *Science*, 257(5067), 212-4 (1992)
DOI: 10.1126/science.1378649

52. C. M. Knudson, G. M. Johnson, Y. Lin and S. J. Korsmeyer: Bax accelerates tumorigenesis in p53-deficient mice. *Cancer Res.*, 61(2), 659-65 (2001)

53. F. Chen: JNK-induced apoptosis, compensatory growth, and cancer stem cells. *Cancer Res.*, 72(2), 379-86 (2012)
DOI: 10.1158/0008-5472.CAN-11-1982

54. Z. Zhan, Y. Ding, R. Zhao, Y. Zhang, H. Yu, Q. Zhou, S. Yang, H. Xiang and W. Wang: Rapid functional divergence of a newly evolved polyubiquitin gene in Drosophila and its role in the trade-off between male fecundity and lifespan. *Mol Biol Evol*, 29(5), 1407-16 (2012)
DOI: 10.1093/molbev/msr299

55. D. Wu, P. M. Tedesco, P. C. Phillips and T. E. Johnson: Fertility/longevity trade-offs under limiting-male conditions in mating populations of Caenorhabditis elegans. *Exp. Gerontol.*, 47(10), 759-63 (2012)
DOI: 10.1016/j.exger.2012.06.010

56. A. Bartke and H. Brown-Borg: Life extension in the dwarf mouse. *Curr. Top. Dev. Biol.*, 63, 189-225 (2004)
DOI: 10.1016/S0070-2153(04)63006-7

57. Y. F. Chen, C. Y. Wu, C. H. Kao and T. F. Tsai: Longevity and lifespan control in mammals: lessons from the mouse. *Ageing Res. Rev.*, 9 Suppl 1, S28-35 (2010)
DOI: 10.1016/j.arr.2010.07.003

58. H. Kurosu, M. Yamamoto, J. D. Clark, J. V. Pastor, A. Nandi, P. Gurnani,

O. P. McGuinness, H. Chikuda, M. Yamaguchi, H. Kawaguchi, I. Shimomura, Y. Takayama, J. Herz, C. R. Kahn, K. P. Rosenblatt and M. Kuro-o: Suppression of aging in mice by the hormone Klotho. *Science*, 309(5742), 1829-33 (2005)
DOI: 10.1126/science.1112766

59. A. Sk, J. V, K. G, U. D and K. P: Declining semen quality among south Indian infertile men: A retrospective study. *J Hum Reprod Sci*, 1(1), 15-8 (2008)
DOI: 10.4103/0974-1208.38972

60. https://www.yahoo.com/news/stress-under-shelling-produces-baby-boom-ukraine-031737960.html. (2017)

Send correspondence to: Rui-An Wang, Department of Pathology, Shenzhen Hospital, Southern Medical University, Shenzhen 518100, China, Tel: 86-15829918163, Fax: 8675523360941, E-mail: ruian79@yahoo.com