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Is early life body weight a predictor of longevity and tumor risk in rats?

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Abstract

Heavy body weight (BW) is thought to be associated with reduced longevity and age-associated diseases, including cancer, both in laboratory rodents and humans. To further investigate the interactions between BW, longevity and spontaneous tumor development, we measured the correlations between BW in early life, BW in middle life, and parameters of life span and tumorigenesis in male and female outbred rats. The data show that BW at the ages of both 3 and 12 months are significant predictors of longevity in rats. Heavier female rats tend to live longer than the lighter female rats, while in male those who were light at 3 months but heavy at 12 month had the best longevity. BW at the age 3 months was not predictive of tumor growth but being heavier at the age of 1 year did confer an increased risk of tumor development for both male and female rats.

Keywords: Body weight; Longevity; Cancer risk; Rat

1. Introduction

Longevity and health are likely to depend on numerous genetic, environmental, and behavioural factors that also influence body weight (BW). In contrast to the observed positive correlation between BW and life span (LS) across mammalian species (Economos, 1980) relatively higher BW within species is thought to be associated with decreased LS. Epidemiological observations provide evidence of increased mortality associated with increasing height, excess BW and obesity (Lee et al., 2001; Samaras et al., 2002; StOnge and Heymsfield, 2003). There are several reports of differences in body size between individuals being associated with differences in longevity within species. In each case, superior longevity is associated with smaller body size. Within a species, the differences in body size depend on differences in single genetic loci, as in the df/df Ames dwarf mice (Brown-Borg et al., 1996; Bartke et al., 2003) and the urokinase knockout α-MUPA mice (Miskin and Masos, 1997). Miller et al. (2000) examined longevity in a series of 15 mouse stocks that were selected over 22 generations for different rate of BW gain and have found that BW at 3, 6 and 12 months are significant predictors of longevity (within stocks). Recently, Miller et al. (2002) have shown that low BW at age 2 months is a predictor of longer LS in mice. It is largely accepted that there is a correlation between greater BW and tumor incidences, the predominant conclusion being that increased BW enhances tumor risk (Gries and Young, 1982; Haseman and Rao, 1992; Haseman et al., 1997; Rao et al., 1990, 1995; Ross et al., 1970; Rao, 1995; Seilkop, 1995). However, some studies have failed to confirm these findings (Eiben and Bomhard, 1999). Calorie restriction (of 30–40%) reduces BW and substantially increases mean and maximum LS in rodents (Weindruch and Walford, 1988). In monkeys, calorie restriction reduced body size and slowed down age-related changes in numerous parameters (Roth et al., 1999a,b; Mattson et al., 2003). Calorie restriction reduces BW and inhibits spontaneous tumor development (Ross et al., 1970, 1983, 1985; Weindruch and Walford, 1988; Mattson et al., 2003).

In this paper we present an analysis of the correlations between BW at 3 months and 1 year, BW gain between 3 months and 1 year, with measures of longevity and tumorigenesis. Longevity is measured by the mean and maximum LS, mortality rate, and mortality rate doubling

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time, MRDT), and tumorigenesis refer to tumor incidence and latency. We have found that the BW at the ages of 3 and 12 months are significant predictors of longevity in rats, with heavier female rats tending to be longer lived, however in males, animals being lighter at the age of 3 months live longer, and being lighter at the age of 1 year live shorter than more heavy males. Fast BW gain reduced LS in females but not in males. The BW at the age of 3 months has no predictor value for tumor risk, however, being heavier at the age of 1 year both males and females have an increased risk of tumor development.

2. Materials and methods

2.1. Animals

Two hundred and 63 males and 206 females of outbred Wistar-derived LIO rats (Anisimov et al., 1989) were bred at Animal Department of N.N. Petrov Research Institute of Oncology. Rats were kept in polypropylene cages (38,5 × 28,5 × 14,5), 6 rats in a cage at a temperature of 22 ± 2 °C. A regimen of 12 h of light and 12 h of dark was followed. The animals received standard laboratory chow and tap water ad libitum.

2.2. Longevity study

All the rats were individually marked and randomly distributed among cages. Males and females were kept separately. Animals were checked daily by animal care personnel and weekly by a veterinarian. The study was carried out in accordance with the regulations for ensuring the humane treatment of animals under the approval of the Committee on Animal Research of the N.N. Petrov Research Institute of Oncology. Weights were recorded in the majority of rats to the nearest gram at monthly intervals from 2 or 3 months of age until the death of the animals. Only rats with a complete BW record were used for the present analysis.

2.3. Pathomorphological examination

The date of each death was registered, and mean LS, the age by which 90% of the animals died, and maximum LS were estimated. All animals that died, or were sacrificed when moribund, were autopsied. At autopsy their skin and internal organs were examined. Neoplasia were classified according to the recommendations of the International Agency of Research on Cancer (IARC) as 'fatal' (i.e. those, that directly caused the death of the animal) or 'incidental' (for cases where the animal died of a different cause) (Gart et al., 1986). All tumors, as well as tissues and organs with suspected tumors, were excised and fixed in 10% neutral formalin. After routine histological processing, tissues were embedded in paraffin. Thin, 5–7 μm histological sections were stained with hematoxylin–eosine and microscopically examined. The experimental group to which the rats belonged was blinded. Tumors were classified according to IARC recommendations (Turusov and Mohr, 1990).

2.4. Statistics

Experimental results were statistically processed (Goubler, 1978). The significance of discrepancies was defined according to Student's *t*-criterion, Fischer's exact method, χ^2-analysis, and the non-parametric criterion of Wilcoxon–Mann–Whitney (Goubler, 1978). For discrepancies in neoplasm incidence to be estimated, an IARC method of combined contingency tables calculated individually for the fatal and incidental tumors (Gart et al., 1986). For survival analysis, Cox's method (Cox and Oakes, 1996) was used. Regression analysis was performed according to Weisberg (1980). All reported test values used in the survival analyses of data are two sided.

2.5. Mathematical models and estimations

The mathematical model used to describe survival is the Gompertz model with the survival function

$$S(x) = \exp\left\{-\frac{\beta}{\alpha}[\exp(\alpha x) - 1]\right\}$$

where parameters α and β are associated with the population rate of aging, and initial mortality rate, respectively. Parameter α is often characterized by the value of MRDT, calculated as $\ln(2)/\alpha$. Parameters for the model were estimated from data using the maximum likelihood method implemented in the Gauss statistical system (Gauss System and Graphic Manual, 1994). Confidence intervals for the aging rate parameter estimates were calculated using log-likelihood functions (Cox and Oakes, 1996).

3. Results

3.1. Sex differences in body weight, life span and tumor incidence

The mean LS for the male rats was 2.5 months shorter than that of the female rats ($p = 0.001$). However, the maximum LS of males was 5.1 months longer than that of females (Table 1). The survival curve for females was shifted to the right of that for males until the age of 800 days when the survival curved intercepted (Fig. 1). Total tumor incidence was slightly but significantly higher for females as compared with males. There was not any difference in the incidence of fatal tumors between the sexes (Table 1). Among benign tumors in females, mammary fibroadenomas, pituitary and thyroid adenomas predominated, whereas

Table 1
Parameters of life span, body-weight and spontaneous tumor incidence in female and male LIO rats

Parameter	Total males	Total females	*P*-value
Number of rats	263	206	
Life span			
Mean LS (M ± m), days	628 ± 17.3	707 ± 15.9	= 0.001
Mean LS (10% of long-living survivors), days	1060 ± 18.5	1098 ± 16.4	
Maximum LS, days	1427	1269	
Mortality rate, α, $days^{-3}$	3.35 (2.74;4.02)	4.34 (3.77;5.13)	
MRDT, days	207 (173;253)	160 (135;184)	
Body weight			
Mean BW of total rats, g: at the age of 3 months	162 ± 4.6	134 ± 4.5	<0.001
Mean BW of total rats, g: at the age of 12–13 months	346 ± 3.7	252 ± 3.3	< 0.001
Mean BW gain of total rats, %	140 ± 6.7	108 ± 6.7	= 0.002
Mean BW of the last 10% of survivors, g: at the age of 3 months	166 ± 15.0	165 ± 11.2*	
Mean BW of the last 10% of survivors, g: at the age of 12–13 months	345 ± 11.0	259 ± 5.8	< 0.001
Mean BW gain of the last 10% survivors, %	137 ± 22.1	68 ± 10.5**	= 0.009
Tumorigenesis			
Number of total tumor-bearing rats	64 (24.3%)	78 (37.9%)	<0.001
Number of fatal tumor-bearing rats	39 (14.8%)	32 (15.5%)	

The difference with the corresponding parameter for the total rats is significant: *$p = 0.016$; **$p = 0.021$.

in males pituitary and thyroid adenomas predominated and no mammary tumors developed (data are not shown).

BW of male rats was increased in comparison to those in female rats at the ages of 3 and 12–13 months and the BW gain in males was higher than that in females. These parameters negatively correlate with the mean LS parameter: males were heavier than females and had shorter mean LS.

It is worth noting that in males, the BW at ages 3 or 12–13 months of the 10% who survived longest, were not different from that of all male rats. However, amongst the 10% of female rats that lived the longest, BW at age 3 months was significantly higher than that of all female rats. The BW gain between 3 and 12 months was significantly less amongst the longest living female rats compared to all female rats.

The regression analysis shows that there is a slight positive correlation between BW at the ages of 3 or 12–13 months and age at death of male and female rats (Fig. 2). BW gain was negatively correlated with longevity in female rats, but not male rats.

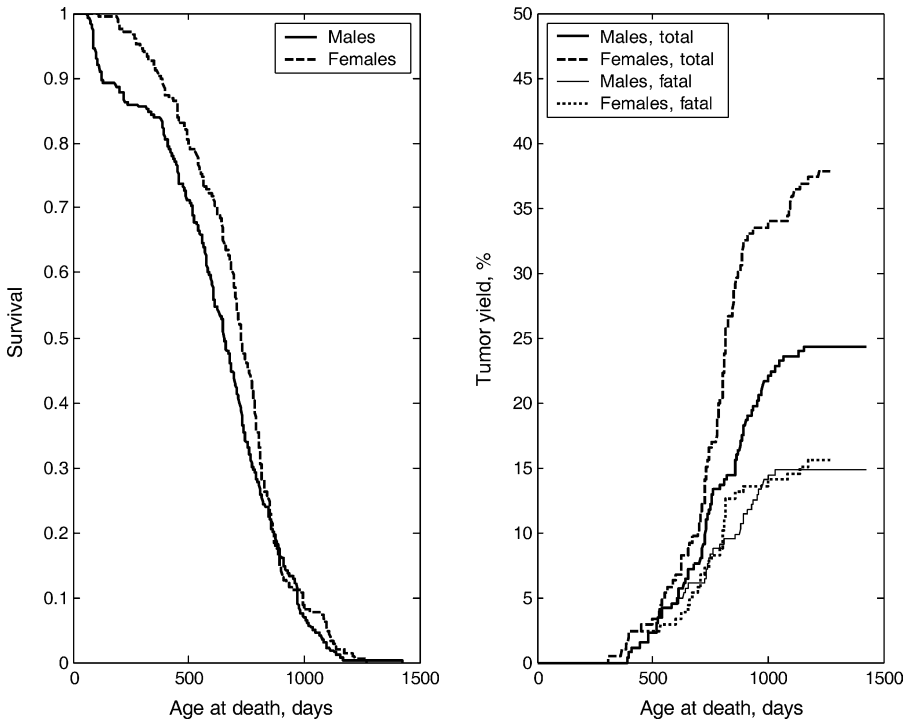

Fig. 1. Survival and tumor-yield curves of male and female LIO rats.

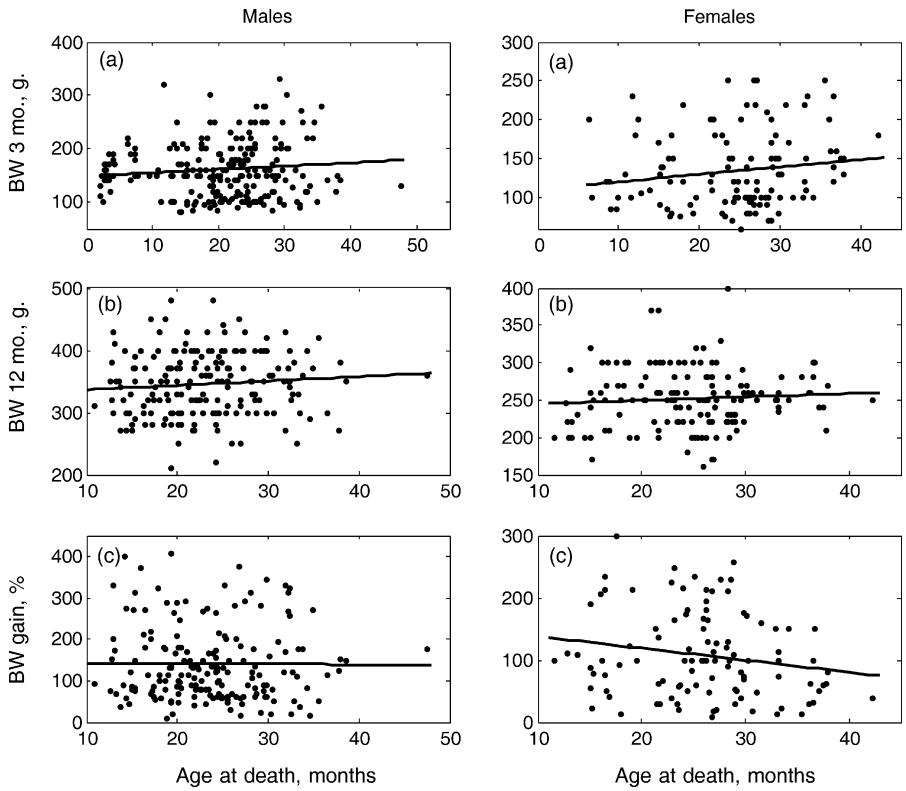

Fig. 2. Association of longevity with body weight in male and female LIO rats. (a) Regression of body weight at the age of 3 months versus age at death; (b) Regression of body weight at the age of 12–13 months versus age at death; (c) Regression of body weight gain between 3 and 12–13 months versus age at death.

3.2. Effect of differences in body weight at the ages of 3 months or 1 year on longevity and spontaneous tumor incidence in rats

There was a slight but significant positive correlation between BW at the ages of 3 or 12–13 months and age at death both in male and female rats (Fig. 2). The regression analysis shows that BW at age 3 months is a better predictor of age of death amongst female rats than BW at age 12 months. Moreover, the BW gain between age 3 and 12–13 months is significantly and negatively correlated with age at death (Fig. 2).

A positive correlation between BW at ages 3 or 12–13 months and the mean and maximum LS was observed in female rats. The BW gain negatively correlated with the mean and maximum LS in females (Tables 2–4).

The heaviest female rats at age 12 months developed more tumors than lighter females, but the incidence of tumors did not depend on the BW at age 3 months or on BW gain (Tables 2 and 3).

Male rats were split into two groups according to their weight at 3 months. 'Light' males were less than 130 g, and 'heavy' males were over 130 g (Table 2). The mean LS of the heavy rats was 100 days shorter that that of the light rats ($p < 0.05$). Conversely, the mean LS of the heaviest males at 3 months (BW > 200 g) was similar to the LS of most light males (< 130 g) but longer than that of males weighing > 130 g (log-rank $= 0.0305$, $p < 0.05$).

Greater BW at 12–13 months was associated with increase in mean LS and maximum LS as compared with lighter males at this age. Survival curves of heavier males were shifted to the right of those for the lighter males (Fig. 3a). However, the log-rank test shows that there is no statistically significant difference between these curves (log-rank $= 0.060$; $p > 0.05$).

The BW gain between the ages of 3 and 12–13 months did not influence mean LS in male rats. The maximum LS was higher in males who were lighter at 3 months and heavier at 12 months. Males who weight light at 3 months but heavy at 12 months had the longest LS; longest than males who where heavy at 3 months or who were heavy at both 3 and 12 months. According to the log-rank test there was no statistically significant differences between all three curves. The heaviest males at 12–13 months and the fastest growing males yielded more tumors as compared to lighter rats (Table 2; Fig. 3b).

In females, there was no correlation between the BW at the age of 3 months and the mean LS of rats (Table 2). However, the maximum LS was shorter and the population aging rate (α) was higher amongst the lighter (< 110 g) females at this age. The log-rank test revealed that the survival curve of light females was significantly to the left of the survival curve of heavy females (log-rank $= 0.0085$

Table 2
Body-weight at the age of 3 and 12–13 months, parameters of life span and spontaneous tumor incidence in male and female LIO rats

Parameters	Males			Females		
	Body weight at the age of 3 months					
	<130 g	>130 g	>200 g	<110 g	>110 g	>140 g
Number of rats	81	158	40	53	66	43
Mean LS (M ± m), days	681 ± 27.1	581 ± 22.1*	718 ± 35.5	703 ± 27.5	759 ± 31.3	790 ± 37.8
Mean BW (M ± m), g	106 ± 1.5	190 ± 5.7*	263 ± 17.6*	93 ± 1.7	168 ± 4.9*	189 ± 5.1*
Maximum LS, days	1427	1156	1065	1026	1269	1269
Mortality rate, α, days $^{-3}$	3.62 (2.81;5.46)	3.45 (2.76;4.25)	5.29 (4.10;7.20)	6.45 (5.01;8.48)	4.18 (3.36;5.1)	4.43 (3.61;5.87)
MRDT, days	191 (127;248)	201 (163;251)	131 (96;169)	108 (82;138)	166 (136;207)	156 (118;192)
No. of tumor-bearing rats	23 (28.4%)	39 (24.7%)	11 (27.5%)	18 (34.0%)	25 (37.9%)	18 (41.9%)
No. of fatal tumor-bearing rats	14 (17.3%)	24 (15.2%)	8 (20.0%)	5 (9.4%)	9 (13.6%)	8 (18.6%)
	Body weight at the age of 12–13 months					
	<320 g	>320 g	>390 g	<225 g	>225 g	>270 g
Number of rats	71	119	43	43	108	41
Mean LS (M ± m), days	669 ± 21.7	728 ± 18.1*	729 ± 26.0	688 ± 27.7	758 ± 18.3*	738 ± 26.6
Mean BW (M ± m), g	293 ± 2.8	378 ± 3.1*	414 ± 3.4*	205 ± 2.4	270 ± 3.0*	302 ± 4.0*
Maximum LS, days	1135	1427	1065	1135	1269	1100
Mortality rate, α, days $^{-3}$	4.94 (4.21;6.16)	4.35 (3.51;6.18)	6.34 (5.46;8.39)	5.75 (4.26;9.66)	5.02 (4.32;6.12)	5.43 (4.66; 6.71)
MRDT, days	140 (113;165)	160 (112;197)	109 (83;127)	121 (72;163)	138 (113;160)	128 (103;149)
No. of tumor-bearing rats	19 (26.8%)	40 (33.6%)	22 (51.2%)*	13 (30.2%)	46 (42.7%)	25 (61.0%)*
No. of fatal tumor-bearing rats	9 (12.7%)	27 (22.7%)	14 (32.6%)*	5 (11.6%)	20 (18.5%)	11 (26.8%)*
	Body weight gain between 3 and 12–13 months					
	<110%	>110%	>170%	<80%	>160%	>200%
Number of rats	83	99	54	44	25	15
Mean LS (M ± m), days	696 ± 19.5	721 ± 20.3	713 ± 29.8	823 ± 32.4	720 ± 27.5*	695 ± 37.3*
Mean BW gain (M ± m), %	66 ± 2.6	202 ± 7.8*	257 ± 8.8*	45 ± 3.2	208 ± 6.7*	229 ± 6.3*
Maximum LS, days	1065	1427	1427	1269	903	867
Mortality rate, α, days $^{-3}$	5.80 (5.14;6.94)	4.06 (3.21;5.57)	3.68 (2.77;6.62)	4.88 (4.06;6.43)	9.67 (7.47;13.4)*	8.94 (6.71;14.6)*
MRDT, days	119 (100;135)	171 (124;216)	188 (106;250)	142 (108;171)	72 (52;93)*	78 (48;103)*
No. of tumor-bearing rats	20 (24.1%)	39 (39.4%)	19 (35.2%)	16 (36.4%)	9 (36%)	6 (40%)
No. of fatal tumor-bearing rats	13 (15.7%)	23 (23.2%)	13 (24.1%)	6 (13.6%)	3 (12%)	2 (13.3%)

The difference with the same parameter for age- and sex-matched rats with minimal BW or BW gain is signficant, $p < 0.05$. **In the brackets − 95% confidential intervals.

as compared to the curve for BW > 110 g and 0.0023 as compared to the curve for BW >140 g; $p < 0.05$).

Females who were more heavy at the age of 1 year (>225 g) had longer mean and maximum LS than lighter females (Table 2, Fig. 4a). The log-rank test revealed a significant difference between survival curves of lighter females and female who weighed >110 g (log-rank = 0.0491, $p < 0.05$). Conversely, the heavy rats have more tumors (log-rank = 0.0203) (Fig. 4b).

BW gain in female rats negatively correlated with mean and maximum LS and with the aging rate (Table 2). The differences between the survival curves for the light rats and for both heavier groups was significant (log-rank = 0.0052 and 0.0028, respectively, $p < 0.05$). The incidence of

Table 3
Results of the regression analysis of body weight against age at death

Sex	Age, months	Regression of body weight vs age at death	
		Slope	Intercept
Male	3	0.626 (0.594;0.658)	148.73 (148.05;149.48)
	12–13	0.700 (0.664;0.736)#	329.74 (328.86;330.62)#
	BW gain	−0.024 (−0.090;0.043)	140.40 (138.78;142.02)
Female	3	0.963 (0.927;0.999)	110.68 (109.75;111.60)
	12–13	0.461 (0.428;0.494)#	240.44 (239.61;241.27)#
	BW gain	−1.921 (−1.985; −1.856)	157.34 (155.62;159.05)

In the brackets − 95% confidential intervals; #-The difference to the sex-matched rats a the age of 3 months is significant, $p < 0.05$.

Table 4
Results of statistical treatment of differences between survival and tumor yield curves of light, medium and heavy rats (Log-rank test)

Sex	Age, months	Life span			Tumor incidence		
		L vs N	L vs H	N vs H	L vs N	L vs H	N vs H
Male	3	0.0602	0.4510	0.0305*	0.4917	0.5899	0.2805
	12–13	0.0600	0.2593	0.7307	0.7014	0.1931	0.0431*
	BW gain	0.2885	0.4281	0.9946	0.3242	0.5799	0.6754
Females	3	0.0085*	0.0023*	0.6141	0.1550	0.1660	0.9803
	12–13	0.0491*	0.6532	0.3489	0.9762	0.0794	0.0203*
	BW gain	0.0052*	0.0028*	0.6016	0.0185*	0.0050*	0.7909

L-light rats; N-normal rats; H-heavy rats. *-Significant at the level of $p < 0.05$.

tumors was not dependent on the BW gain although faster growing female rats developed tumors earlier than those who grew more slowly (log-rank = 0.0185) (Fig. 4b).

There was a slight but significant positive correlation between BW at ages 3 or 12–13 months and age of death in male rats (Fig. 2). The regression analysis shows that BW at age 3 months is a better predictor of age at death than BW at age 12–13 months. However, the BW gain between the ages of 3 and 12–13 months negatively correlated with age of death (Fig. 2).

Positive correlation between BW at 3 or 12–13 months and both the mean and maximum LS was observed in female rats. Conversely, BW gain negatively correlated with both the mean and maximum LS in females (Table 2; Fig. 2). Females who were heaviest at 12 months developed more tumors than lighter females, although the incidence of tumors did not depend on the BW at 3 months or on BW gain. (Table 2).

4. Discussion

In Table 5 we summarised our findings regarding BW at different ages and parameters of LS in male and female rats. In general, heavy BW at the age of 3 months correlated negatively with longevity in males but positively in females. A positive correlation between BW at age 12 months and longevity was evident in both males and females. The BW gain between ages 3 and 12 months correlated negatively with LS in females but there was no correlation for males. Heavy BW at 3 months negatively correlated with tumor incidence, and BW at 12–13 months positively correlated

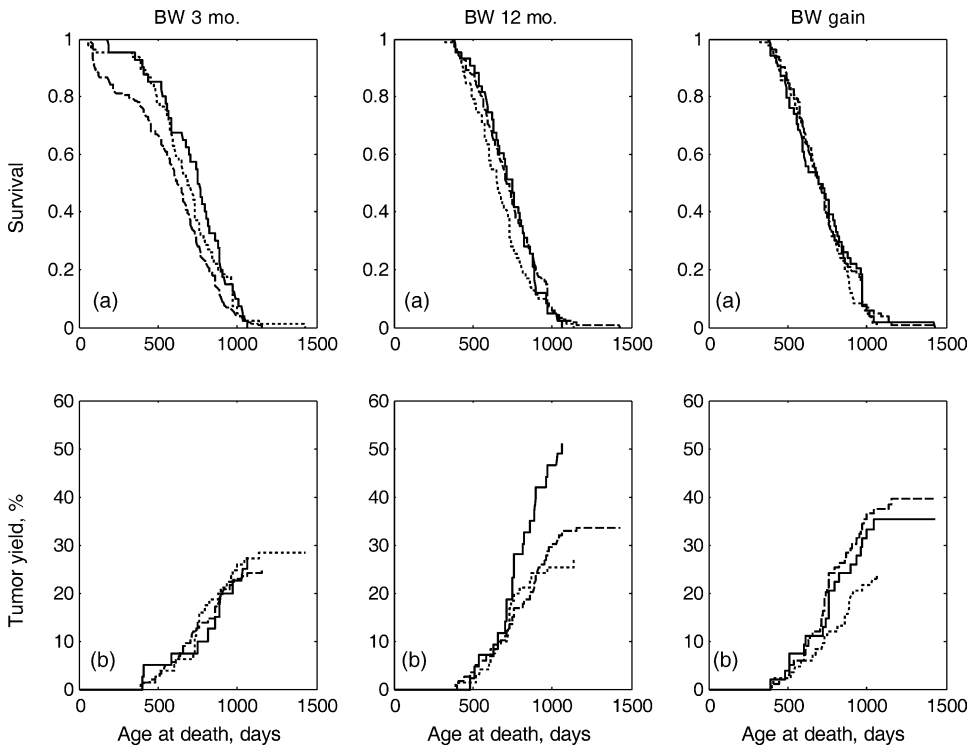

Fig. 3. Survival and tumor-yield curves in male LIO rats with different body weight at various ages. (a) Survival function; (b) Tumor incidence.

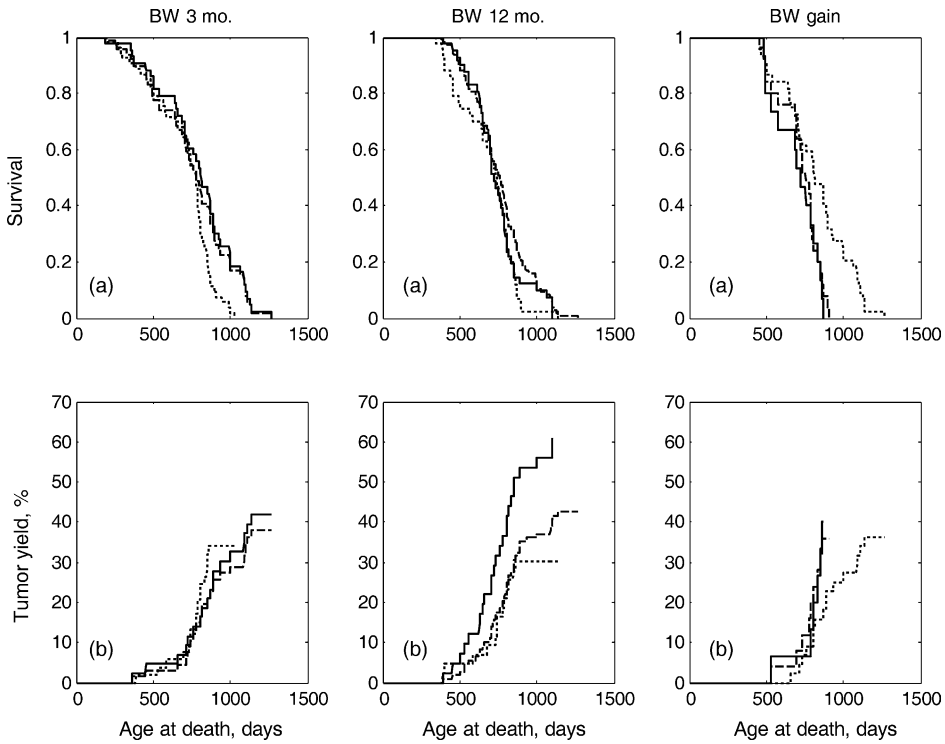

Fig. 4. Survival and tumor-yield curves in female LIO rats with different body weight at various ages. (a) Survival function; (b) Tumor incidence.

with tumor incidence, both in male and female rats. BW gain between 3 and 12 months was not correlated with tumor incidence.

Calorie restriction is the most effective way to increase LS in a variety of animal species, including mammals (Weindruch and Walford, 1988; Mattson et al., 2003). Calorie restriction has also been shown to be very effective in preventing cancer (Weindruch and Walford, 1988; Hursting and Kari, 1999). BW decline is one of the main characteristics of animals maintained on a calorie restriction diet. Genetic manipulations leading to dwarfism is followed by either a significant increase in LS and tumor latency or by a decrease in tumor incidence amongst mice (Bartke et al., 2003). Miller et al. (2000, 2002) stressed that low BW as early as 2 months of age is a predictor of longer LS. The authors noted that the association is seen in both male and female mice, although males are substantially heavier throughout life. The inverse correlation between BW and survival is described by Roe et al. (1995) and Turnbull (1985) for Wistar and Sprague–Dawley rats. There are numerous reports of positive correlations between heavy BW and tumor incidence (Gries and Young, 1982; Haseman and Rao, 1992; Haseman et al., 1997; Rao et al., 1990; Roe et al., 1995; Ross et al., 1970; Seilkop, 1995). However, the relationship between BW and longevity is not entirely consistent with LS effects. Ingram and Reynolds (1983) have shown that the reduction of dietary protein from a normal level (8 from 20%) was associated with reduced BW but was not associated with a significant increase in LS. Reviewing the available data on the intra-group correlations between BW and LS, Ingram and Reynolds (1987) concluded that in general, the existence and direction of

Table 5
Correlations of some parameters with heavy body weight in male and female LIO rats

Sex	Age	Mean LS	Maximum LS	Mortality rate, α	MRDT	Survival Curves	Tumor incidence	Regression slope
Male	3	↓	↓	=	=	=	=	↑
	12–13	↑	↑	=	=	=	↑	↑
	BW gain	=	↑	=	=	=	↑	↓
Female	3	↑	↑	↓	↑	→	=	↑
	12–13	↑	↑	=	=	→	↑	↑
	BW gain	↓	↓	↑	↓	←	↑	↓

Only statistically significant results are given; ↑, The increase in the parameter in heavier animals; ↓, The decrease in the parameter in heavier animals; =, No difference between heavy and light animals; →, Significant shift of survival curve for heavy animals to right; ←, Significant shift of survival curve for heavy animals to left.

significant correlations between BW and LS was dependent upon age and genotype. The authors found positive correlations between BW at the middle of life and LS in Wistar rats. Everitt and Webb (1977) found a significant positive correlation between LS and BW at the age of 400 days while BW at other ages was not significantly correlated with LS. Weindruch et al. (1986) found correlation between LS and BW at weaning, 5, 10, 15 and 22 months within groups of female C3B10RF$_1$ mice on ad libitum and calorie restricted regimens. The only correlations that were significant were positive and between LS and BW after 5 months. While Ingram and Reynolds (1987) stressed that the most prevalent significant correlation between BW and LS appeared to be positive in direction within male rodent species, our findings show that greater BW at 3 months or 1 year is a significant predictor of longevity for female rats as well as male rats. Wirth-Dzeciolowska and Czuminska (2000) have analysed the differences between longevity and the aging process in two lines of mice selected divergently for BW for over 90 generations. It was shown that heavy females live longer than light females and that light male mice lived 30 days longer than heavy ones. Our results are in agreement with these observations. It is worth noting that in females the rate of BW gain is a significant predictor of reduced longevity while excess BW at 12–13 months is a predictor of increased tumor risk both in female and male rats.

There is abundant evidence that obesity is associated with excess morbidity and mortality in humans (StOnge and Heymsfield, 2003). In contrast, extreme leanness is also associated with excess mortality (Samaras and Elrick, 1999). Instead of a linear correlation between BW and LS, some investigators of human populations have emphasized the curvilinear nature of the relationship (Waaler, 1988; Ingram and Reynolds, 1987). Andreas et al. (1985) has studied the relationship between the ideal BW in terms of lowering mortality risk and age and concluded that the ideal BW increases linearly with adult age. Ingram and Reynolds (1987) have discussed two possible explanations for this observation. One deduction might be that in late ages, relatively heavier persons face a lower mortality risk than their lighter counterparts. The other deduction is that gaining weight with age might reduce mortality risk. Based on several literature reviews, Andres et al. (1985) concluded that little evidence exists to support an inverse relationship between adult BW and mortality risk.

In a comprehensive review on the relationship between BW and longevity within laboratory rodent species, Ingram and Reynolds (1987) suggested that the relationship between BW and LS is curvilinear. This model attempts to accommodate the existence of genotypes. The authors suggested that for genotypes prone to leanness, heavier BW should be positively correlated with LS, whereas in genotypes prone to obesity, BW should be negatively correlated with LS. In recent intensive and comprehensive review on genetic mouse models of extended LS, Liang et al. (2003) concluded that many of the genetic manipulations that lead to increased LS result in reduced growth and small body size. This is consistent with data that reduced body size in dogs and mice correlated with longevity (Miller, 1999).

Recently, Fontaine et al. (2003) estimated the expected number of years of life lost due to being overweight and obesity across the LS of an adult human. Among white people, a J- and U-shaped association was found between being overweight or obese and the number of years of life lost. For any given degree of excess weight, younger adults generally lost more years than did older adults. The maximum number of years lost for obese white adults aged 20–30 was 13 for men and 8 for women. Among black adults over 60 years old, being overweight or moderately obese was not generally associated with an increased loss of LS. However, black males at younger ages with severe levels of obesity lost a maximum of 20 years, and the equivalent figure for females was 4 years. Our results are not contradictory to these observations and are in agreement with the conclusion drawn by Ingram and Reynolds (1987) that there is no evidence that thinner is necessarily better for survival. Our data are in agreement with observations that heavy BW at midlife increases cancer risk, however.

The potential link between aging and insulin/IGF-1 signaling has attracted substantial attention during last years, on the basis of evidence including age-related increase in incidence of insulin resistance and type 2 diabetes in accelerated aging syndromes and LS extension by caloric restriction in rodents. Concomitant reduction in plasma insulin and plasma glucose levels, which implies increases sensitivity to insulin, emerges as a hallmark of increased longevity (Bartke et al., 2003; Longo and Finch, 2003; Tatar et al., 2003). Harper et al. (2003) have shown that long life span was predicted by low levels of leptin at age 4 months in female genetically heterogenous mice, and by low levels of IGF-1 at age 15 months, in males. It is well known that excess of BW or, more precisely, a constant of a fat in the body, accomplishes with the increase in serum insulin and reduction of susceptibility tissues to insulin (Dilman, 1994). Hyperglycemia is an important aging factor involved in generation of advanced glycosylation end-products (AGEs) (Facchini et al., 2000; Ulrich and Cerami, 2001). There are evidence that hyperinsulinemia favors accumulation of oxidized protein by reducing its degradation as well as facilitates protein oxidation by increasing steady-state level of oxidative stress (Xu and Bard, 1999; Facchini et al., 2000). Untreated diabetics with elevated glucose levels suffer many manifestations of accelerated aging, such as impaired wound healing, obesity, cataracts, vascular and microvascular damage (Dilman, 1994). Overweight, hyperlipidemia, and hyperinsulinemia are also an important factors in the development of metabolic immunodepression (Dilman, 1994). It was shown that centenarians have a preserved glucose tolerance and sensitivity to insulin as well as lower degree of oxidative stress and better

immune status as compared to aged persons (Paolisso et al., 2001; Barbieri et al., 2003). It is important to stress that hyperinsulinemia is an important factor not only in aging but also in the development of cancer (Dilman, 1994; Colangelo et al., 2002; Gupta et al., 2002; Anisimov, 2003). It seems important to evaluate the predictive role of serum insulin level or, better, susceptibility of tissues to insulin, at young age for longevity and cancer risk in rats and humans.

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