INTERNATIONAL MASTER ON ANIMAL BREEDING AND REPRODUCTION BIOTECHNOLOGY

COMPARING LONGEVITY TRAITS IN FOUR MATERNAL LINES OF RABBITS

AYMAN GAMAL FAWZY EL NAGAR

SUPERVISOR

Prof. Dr. Manuel Baselga Izquierdo

CO-SUPERVISOR

Dr. Juan Pablo Sánchez Serrano

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ABSTRACT

This study was conducted in four Spanish maternal lines of rabbits (A, V, H and LP) reared in the closed nucleus of selection located in the farm of the Department of Animal Science, Polytechnic University of Valencia. Data for this study were collected during the program of selection of maternal lines of rabbits from September 1980 to March 2011.

The main objective of this work was to compare the longevity trait in four maternal lines of rabbits (A, V, H and LP) selected for litter size at weaning but founded on different criteria. The comparison has been done at their foundation time using the complete pedigree file and the complete data set performed from their foundation until March, 2011. The second objective of this study was to compare the lines at fixed times. The fixed times of comparison were from March, 1997 to September 1998 for A, V and H lines, and from September, 2009 to March, 2011 for A, V and LP lines.

The results of the present study could be summarized as follows:

1- The estimated additive genetic variance of longevity resulted from the use of the complete data set (12693 does and 14805 record in the pedigree file), and the complete genetic model was 0.195 with standard deviation of 0.03. This estimate corresponds to an effective heritability of 0.163, while corresponds to an equivalent heritability of 0.104 considering the proportion of uncensored data as 59.57 % of the whole data set.
2- Regarding the comparison of longevity between the lines A, V, H, and LP at their foundation using the complete genetic model and the complete data set from the foundation of the four lines until March, 2011. The lines V, H and LP showed a significant superiority over line A. The greatest difference was between the lines A and LP, while the differences between line V and both of H and LP lines were small and non significant. These differences between lines may be attributed to the history of foundation of each line

where all of them were founded on different criteria but all selected for litter size at weaning.

3- Regarding the comparison between lines at fixed times, the first comparison was between lines A, V, and H and the selected data were performed during the period from March, 1997 to September, 1998. It is shown that line A had a risk of culling or death greater than lines V and H. the same trend as in the case of the comparison at the foundation time of these lines, while the differences between lines V and H were non significant. The second comparison was between lines A, V, and LP and the selected data set were performed during the period from September, 2009 to March, 2011. This comparison reflects the current situation of these three lines, it is shown the inferiority of the line A over the two other lines (the same trend as the anterior comparison), this means lower longevity of line A which had limited capacity to face the opposite risk factors. No significant difference between the V and LP lines has been founded.

4- The observed differences between lines during these periods were much lower than those at the foundation time due to in part to the main cause of these differences in the genetic level of the contemporary animals compared to the founders.

5- Given the expected differences between lines at the two fixed times that computed using the complete genetic model (which included the additive genetic value of animals), showing that the observed and expected values of the hazard are relatively similar. This means that the complete model used in the analysis was suitable to describe this longevity data set.

RESUMEN

Este estudio se realizó en cuatro líneas maternales españolas de conejos (A, V, H y LP) alojadas en el núcleo de selección de la granja experimental del departamento de Ciencia Animal de la Universidad Politécnica de Valencia. Los datos de este estudio se recogieron durante el programa de selección de las líneas maternales de conejos a partir de septiembre de 1980 hasta marzo de 2011.

El objetivo principal de este estudio consistía en comparar la longevidad de las cuatro líneas maternales de conejos (A, V, H y LP) seleccionadas para el tamaño de camada al destete pero fundadas sobre distintos criterios. La comparación se hizo a partir del momento de la fundación de estas líneas utilizando el pedigrí completo y los datos obtenidos hasta marzo de 2011. Otro objetivo de este trabajo era comparar las líneas a períodos de tiempo fijos que fueron de marzo de 1997 a septiembre de 1998 para las líneas A, V y H y de septiembre de 2009 a marzo de 2011 para las líneas A, V y LP.

Los resultados obtenidos mostraron que la variación genética aditiva considerada de la longevidad resultante de la utilización de los datos de 12693 hembras y el modelo genético completo era 0.195 con una desviación típica de 0.03. Esta estimación corresponde a una heredabilidad efectiva de 0.163 y corresponde a un heredabilidad equivalente de 0.104 que considera la proporción de los datos no censurados como un 59.57% de datos totales. Las líneas V, H y LP presentaron una longevidad significativamente superior a la línea A, pero al contrario no se observó diferencias significativas entre la línea V y las dos líneas H y LP.

Por lo que se refiere a la comparación entre líneas a tiempo determinado, para la primera comparación estaba entre las líneas A, V, y H se observó que el riesgo de eliminación o muerte fue mayor en la línea A que las líneas V y H. lo mismo que se apreció para el caso de la comparación en el momento de fundación de estas líneas, mientras que las diferencias entre líneas V y H eran no significativos. Durante el segundo periodo de comparación se consideraron las

líneas A, V, y LP. Esta comparación refleja la situación actual de las tres líneas, se observó una inferioridad de la línea A lo que corresponde a una reducción de la longevidad de esta línea debida a la baja resistencia a los factores del riesgo. No se observaron diferencias significativas entre V y LP. Las diferencias observadas entre líneas durante estos períodos de comparación han sido más bajas que aquéllas observadas durante su fundación debido a una correlación genética positiva entre prolificidad (criterio de selección) y longevidad.

A partir de las estimas del modelo completo se predijeron de manera precisa las diferencias observadas en los dos periodos considerados lo que confirma que el modelo utilizado en este análisis es apropiado para el análisis de este conjunto de datos longevidad.

Résumé

Cette étude a été menée au niveau de quatre lignées maternelles de lapines espagnoles (A, V, H et LP) logées dans le noyau de sélection de la ferme expérimentale du département de production animale de l'université polytechnique de Valence. Les données utilisées dans cette étude ont été collectées au cours du programme de sélection des lignées maternelles de lapins á partir de septembre 1980 jusqu'au mars 2011.

L'objectif principal de cette étude était de comparer la longévité des quatre lignées maternelles de lapines (A, V, H et LP) sélectionnées pour la taille de portée au sevrage mais fondé sur des différents critères. La comparaison a été faite á partir du moment de la fondation de ces lignées en utilisant le pédigrée complet et les données obtenues jusqu'au mars 2011. Autre objectif de ce travail était de comparer les lignées à des périodes de temps bien déterminées, durant les trois dernières années, qui étaient de mars 1997 à septembre 1998 pour les lignées A, V et H et de septembre 2009 à mars 2011 pour les lignées A, V et LP.

Les résultats obtenus ont montré que la variance génétique additive estimée de la longévité résultante de l'utilisation des données de 12693 femelles et le modèle génétique complet était 0.195 avec une déviation standard de 0.03. Cette estimation correspond a une héritabilité effective de 0.163 ce qui correspond aussi a une héritabilité équivalente de 0.104 tout en considérant la proportion des données non utilisées comme 59.57 % de données totales. Les lignées V, H et LP ont présenté une longévité significativement supérieure á la lignée A mais au contraire on n'a pas observé des différences significatives entre la lignée V et les deux lignées H et LP.

Concernant la comparaison entre lignées à temps déterminé, la première comparaison a été faite entre les lignées A, V, et H et on a observé que le risque de reforme ou de mortalité est plus grand pour la lignée A que pour les lignées V et H. La même tendance a été observée dans le cas de la comparaison au moment de la fondation de ces lignées, tandis que les différences entre lignées V et H étaient non significatives. La seconde comparaison a été faite entre les lignées A, V, et LP. Cette comparaison reflète la situation actuelle des ces trois lignées, du fait on a observée une infériorité de la lignée A et par conséquent une réduction de la longévité de cette dernière due a sa sensibilité aux facteurs de risque. Des différences non significatives ont été observées entre V et LP. Les différences observées entre lignées durant ces périodes étaient plus

faibles que celles au moment de leur fondation due à une corrélation génétique positive entre la prolificité (critère de sélection) et la longévité.

Les estimations du modèle complet ont permis d'interpréter d'une manière précise les différences entre lignées pendant les deux périodes considérées ce qui confirme que le modèle utilisé dans cette analyse est approprié pour l'analyse de l'ensemble des données de la longévité.

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1. INTRODUCTION

1.1. Definitions of rabbit doe longevity and cumulative production.

Longevity of rabbit doe (length of the doe's productive life, **LPL**) is defined as the number of days between the date of the first positive diagnosis of pregnancy and the date of culling or death **(Sánchez et al., 2004)** this definition is similar to the one implanted in dairy cattle by **Roxastöm et al. (2003)**.

Another definition of rabbit doe longevity is the number of days between the first mating and the date of death/culling or censoring of the female **(Piles et al., 2006a; Sánchez, 2005)**. Another one is due to **Garreau et al. (2005)**, the number of artificial inseminations a female is subject to.

When longevity definition is independent of the level of production it is named functional longevity, in general this is the type of longevity that has been considered, does in the published studies were never culled on account of their production results, thus the length of doe productive life represents functional longevity **(Sánchez, 2005 & 2008** and **Piles et al., 2006b)**. Similarly, **Ducrocq (1994**) defined functional longevity in dairy cows as the ability to delay involuntary culling, i.e. culling based exclusively on non productive reasons.

Longevity in dairy and beef cattle has been studied with another definition, stayability. This is a binary trait representing whether an animal has reached some fixed parity or age. In the beef cattle case, it represents the probability that a cow is in the herd at given years of age, in general the most common age is six years which is when most cows would reach a positive net present value, this is conditional to the cow been in the herd since two years old, (**Cowley, 1998**). Stayability provides the beef cattle producer with an estimate of how long a sire's daughters will stay in the herd.

Cumulative production is another indication of longevity which was defined as the total number of young weaned by a doe during her lifetime (from the first positive pregnancy test until death or culling). With this definition, the trait is subjected to right censoring, because in the case of does alive at the end of the period of study, it is only known that the real value for this trait would be greater than the one recorded until that time (**Sánchez et al., 2008**). Right censoring it is also a very important feature of **LPL** in animal production, and similarly to cumulative production it occurs when an animal is removed before failure can be observed.

1.2. Importance of longevity.

In general replacement costs in animal production represent a relatively high component of production costs, especially when culling is involuntary (e.g., due to death or fertility problems). Therefore animal scientists are often studying ways to increase the average length of productive life of domestic farm animals or to decrease the frequency of involuntary culling. For the case of rabbit for meat production, the replacement rate is about 120% yearly (**Rafel et al., 2001**) with about 50% of the dead or culled does replaced during their first 3 parities (**Rosell, 2003**). The main problems associated with this high replacement rate are the replacement cost of the does itself, the greater frequency of less mature females (young does are still growing and are less immunologically mature at parturition, showing lower litter size and more health problems), and sometimes the management and pathological problems related to introduction of animals from other farms (**Piles et al., 2006a**). Therefore selective breeding to increase the length of productive life could be an alternative to reduce costs attributed to replacements and then increase the profitability of rabbit does.

1.3. Survival analysis.

Historically survival analysis was a statistical method originally developed for research in medicine and engineering, to study the time to an event of interest, when this event is the death or culling we are delaying with longevity data. Survival analysis combines information both from uncensored (the animal was dead or culled) and censored (the animal is still alive or productive at the end of the experiment) records in a single analysis, this statistical technique enables a proper statistical treatment of censored records and also it accounts for the nonlinear characteristics of longevity records.

Regarding censoring, as it has been previously mentioned, it is applied when an observation is incomplete, but the reason for this lack of information should be random. Or at least the cause of the censoring must be independent of the event of interest. Censored data provide partial information in the sense that we only know that the event had not occurred when the records were obtained (**Klein and Moeschberger, 1997**); for this reason censored records should be included in the analysis because removing them or treating them as uncensored records could lead to biased estimates (**Guo et al., 2001**). This type of censoring is called right censoring that is the important type in studies of **LPL** in animal production but there are other types. Thus if the failure occurs prior to a given time in which we only know the end point and do not know the origin point this type is called left censoring. Another type of censoring named double censoring is a combination of left and right censoring in this case the exact time when the event occurs is not known precisely, but an interval bounding this time is known. Right censoring can occur because an animal is removed before failure can be observed, or because the animal is subject to any factor that avoid observing the event of interest, in this case death or culling because of involuntary reasons.

Studying longevity data requires special statistical treatment for three main reasons: 1) the distribution of survival time is rarely known and in most cases, extremely skewed; 2) for part of the observations, only a lower bound of survival time is known e.g., for individuals still alive at the end of the study period (right censoring); 3) the independent variables influencing survival time may themselves vary with time (e.g., current milk production, herd size, disease occurrence). Survival analysis techniques allow considering them.

Longevity data can be defined using a set of functions of the time to the event of interest variable.

(1) Cumulative distribution function, F(t) = Prob [T < t] where T represents the actual failure time of an individual from a homogenous population, as a positive random variable that assume to be continuous.

(2) Density function, f(t) = $\lim_{dt\to 0}\frac{\Pr ob(t \le T < t+dt)}{dt} = \frac{dF(t)}{dt}$

Where the density function is the limiting probability that failure will occur between t and t + dt.

(3) Survivor function, S(t) = Prob [T ≥ t] = 1 – F(t), where S(t) is the fraction still alive at the time t, $\frac{dF(t)}{dt} = -\frac{dS(t)}{dt}$ = f(t).

(4) Hazard function, h(t) which specifies the instantaneous failure (= death or culling) rate at the time t, conditional upon survival up to t. This ratio is always positive and can be greater than 1. The hazard function measures the risk of dying (failure rate), failing (failure rate), being culled (culling rate) among animals alive at the time t. The hazard function plays an important role in survival analysis in particular in the modelling of survival curves. Where h(t) =

$$\lim_{dt\to 0}\frac{\Pr ob(t \le T < t+dt|\ \mathrm{T}\ \ge\ \mathrm{t}\ )}{dt} = \frac{f(t)}{S(t)} = -\frac{d\log S(t)}{dt}$$

From the previous equations it could be concluded that the survival and hazard functions provide alternative but equivalent characterizations of the distribution of T. Given the survivor function, we can always differentiate to obtain the density and then calculate the Hazard. Given the hazard, we can always integrate to obtain the cumulative hazard and then exponentiate to obtain the survivor function. In particular S(t) = $\exp\left\{-\int_0^t h(u)du\right\}$ = exp (- H (t)), where H(t) = $\int_0^t h(u)du$ is the Cumulative hazard function. The last relationships are essential to remember because they explain why modelling of the hazard function is not fundamentally different from modelling of the density function. An important extension needed at this point is the inclusion of random censoring, for each animal i, there are a failure time T_i and a censoring time C_i but only one is observed. T_i for an uncensored observation (in this case, we know that censoring would have occurred after t= T_i), C_i for a censored observation (in the case, we know that death would have occurred after $t= C_i$). Finally the random variable being analyzed is $Y_i= \min (T_i , C_i)$, i.e., the time at which the first one of these two events (failure and censoring) occurs. In the case of random censoring it is assumed that T_i and C_i are independent. Then the knowledge of the distribution of the censoring time C_i does not bring any information about the distribution of T_i and it can be shown that the contribution to the likelihood is for uncensored records is the value of the density function at failure time, $f(y_i)$, and for censored records the value of the survivor function at censoring time, $S(y_i)$.

All this functions can be defined throughout a number of parametric models, the most commonly used are the Exponential and Weibull, but also Gamma, Generalized Gamma, Gompertz, Log-Logistic and Log-Normal could be used **(Kalbfleisch** and **Prentice, 1980)**, and it would be needed to estimate the parameters for each one of these models. But also non-parametric methods can be used to estimate the form of the previously described functions, for example the Kaplan-Meier estimator.

It can be said that the hazard function determines the type of distribution to be used. For example, If the hazard function it is assumed to stays constant over time ($h(t) = \lambda$ = constant, $\lambda > 0$) this means that the changes of failure at any time are the same regardless of how long the subject has been on test (memoryless property). For this type of hazard function the parametric model to be used is the exponential in which the survivor function $S(t) = \exp (-\int_0^t h(u)du) = \exp (-\lambda t)$, and the density function is of the form $f(t) = h(t).S(t) = \lambda \exp (-\lambda t)$. If the hazard functions is not constant, means that the changes of failure at any time are not the same. One of the most common parametric models is the Weibull distribution. The Weibull survivor function is a very simple modification of the exponential one, $S(t) = \exp (-(\lambda t)^{\rho})$ where $\lambda > 0$ and $\rho > 0$ in this case, if $\rho = 1$ then $S(t)$ reduces to the exponential survivor function, if $\rho > 1$ an increasing hazard is observed with time and if if $\rho < 1$ a decreased hazard is observed with time. The density function is of the form $f(t)$

$= h(t).S(t) = \lambda \rho (\lambda t)^{\rho-1} \exp(-\lambda t)^{\rho}$ in which the hazard function $h(t) = \lambda \rho (\lambda t)^{\rho-1}$. The choice of the Weibull distribution results from the simplicity of the Weibull survivor function and the model has the advantage of easy extension to mixed survival models that can include correlated random effects such as relationship among individuals (**Ducrocq and Casella, 1996**).

Table(1): Parametric distributions used in survival analysis.

Distribution	**f(t)[a]**	**h(t)[b]**	**H(t)[c]**	**S(t)[d]**
Exponential	$\lambda \exp(-\lambda t)$	λ	λt	$\exp(-\lambda t)$
Weibull	$\lambda \rho (\lambda t)^{\rho-1} \exp(-\lambda t)^{\rho}$	$\lambda \rho (\lambda t)^{\rho-1}$	λt^{ρ}	$\exp[-(\lambda t)^{\rho}]$

[a] f(t) density function, [b] h(t) hazard function, [c] H(t) cumulative hazard,
[d] S(t) survivor function.

Non parametric analysis allows the user to analyze data without assuming an underlying distribution. The ability to analyze data without assuming an underlying life distribution avoids the potentially large errors brought about by making incorrect assumptions about the distribution. On the other hand, the confidence bounds associated with non-parametric analysis are usually much wider than those calculated via parametric analysis, and predictions outside the range of the observations are not possible. One of the most common non-parametric methods is the Kaplan-Meier estimator of the survivor function named as product limit estimator, this estimator is in general used as a descriptive method of data in order to check the suitability of parametric models. A non-parametric estimate of the survivor curve S(t) can be obtained by describing the probabilistic definition of S(t) as a product of conditional probabilities:

$$S(t) = \text{Prob}[T \geq t]$$

$$= \text{Prob}[T > T_{[1]}] \text{ X } \text{Prob}[T > T_{[2]}] \mid T > T_{[1]} \ldots\ldots \text{ X } \text{Prob}[T > T_{[K]} \mid T > T_{[k-1]}]$$

Where $T_{[k]}$ is the largest observed failure time prior to t.

A estimator of each conditional probability Prob[T > $T_{[K]}$ | T > $T_{[k-1]}$] is : number still alive just after $T_{[k]}$ / number still alive just prior to $T_{[k]}$ is $\left(\frac{n_k - d_k}{n_k}\right)$

This estimator, combined with the probabilistic definition of S(t), leads to the following non-parametric estimator of the survivor curve:

$\hat{S}(t) = \hat{S}_{KM}(t) = \prod_{k|T[k]<t} \left(\frac{n_k - d_k}{n_k}\right)$

This expression is known as the product limit estimator or the Kaplan-Meier estimator **(Kaplan and Meier, 1958)**. If there is no censoring, $\hat{S}_{KM}(t)$ is simply equal to 1 minus the usual empirical cumulative distribution (1 – F (t) = a non-parametric estimate of the cumulative distribution function).

In addition to describe for an entire population the functions previously mentioned, as an overall mean of an homogenous population, the survival analysis may also include explanatory variables, that could define sub-population for example different genetic groups. But in reality we often interested in how these explanatory factors differ in their hazard than in how the hazard actually change over time. Let **x** = $(x_1, \ldots.. x_n)$, be a vector of explanatory variables which failure time may depend on and **b** = $(b_1, \ldots\ldots b_n)$, be a vector of regression variables. The hazard function of an individual with variables **x** can then be considered as, h(t, **x**) = $h_0(t) . \exp(\mathbf{x}'\mathbf{b})$. The term $h_0(t)$ is called as the baseline hazard function and does not depend on the covariates, and the second term describes the importance of the covariates. Thus, the second term acts multiplicatively on the baseline hazard function. The relationship between two different individuals having covariates x_a and x_b is constant over time, these two animals will have the hazard function $h(t, x_a) = h_0(t) \exp(x_a\ b)$ and $h(t, x_b) = h_0(t)\exp(x_b\ b)$ respectively, and the ratio will be $h(t, x_a) / h(t, x_b) = h_0(t)\exp(x_a\ b) / h_0(t)\exp(x_b\ b) = \exp((x_a - x_b)b)$, which does not depend on time. Thus the relationship between any covariates is always constant, and this is why these models called *proportional hazard models*. This has important consequences on the estimation procedures, which get simplified appealing to this property. The baseline hazard function can be modeled with different distributions for example Exponential or Weibull, depending on our assumptions regarding how the average of hazard of the changes with time. But the baseline can also be kept completely arbitrary as in the semi-parametric model, which is called the *Cox model* **(Cox, 1972)**. Fitting the proportional hazard models includes the estimation of estimates of the unknown coefficients b_1, b_2,…b_n and if a parametric form is assumed for the baseline it is also needed to estimate the parameters describing this function. In the case of the Cox model the vector **b** is estimated with Cox partial likelihood, which is the part of the full likelihood that does not depend on the baseline, thus not any parameter regarding the baseline will be considered during the estimation, but the baseline effect if has been accounted for. This partial likelihood has the same properties as those obtained working with true likelihood, e.g. is asymptotically unbiased and follows a multivariate normal distribution with variance-covariance matrix equal to minus the inverse of the Hessian of the log-partial likelihood function. This property is used to contrast confidence interval and to perform hypothesis test.

As it has been mentioned the proportionality between risk is an important feature, but there could exist situation when it is not fulfilled, one situation is when different baseline hazards function characterize different subset of animals, and the other happened when during the entire life of an individual the levels acting of the different factors acting on this individual change with time. Both situations can be accommodated in a straightforward way either in parametric regression models or in the Cox model by performing stratified analyses or by including time-dependent covariates **(Ducrocq, 2007)**.

A further extension of the proportional hazard models of regression is the inclusion of random effects. In survival analysis terminology the random effects are called frailty terms, which are an unobserved random proportionality factors that modifies the hazard function of an individual, or of related individuals. In essence, the frailty concept goes back to work of **Greenwood and Yule (1920)** on "accident proneness’’. The term frailty itself was introduced by **Vaupel et al. (1979)** in univariate survival models and the model was substantially promoted by its application to multivariate survival data in a seminal paper by **Clayton (1978)** (without using the notion "frailty") on chronic disease incidence in families. Proportional hazard models, whether they are parametric or not can be extended to include random effects. When the frailty term is defined separately for each individual the frailty component extracts part of the unobserved variation between individuals (**Vaupel et al., 1979, Aalen, 1994, Damgaard et al., 2006**) and therefore allows for a correction of the possible discrepancy between the variance of the observations and the one specified by the model. When the term of frailty is defined for a group of individuals, for example all daughters of a sire it describes the shared unobservable characteristics which act on the hazard of each member of the group (**Anderson et al., 1992**, **Klein et al., 1992, Ducrocq, 2005**). In all cases, a simple transformation allows the inclusion of the frailty term in the term of $e^{x'\beta}$ of the usual regression models. In general for the prediction of frailty terms Bayesian approaches have been adopted, regarding the distribution of the frailty terms as a prior assumption in the analysis. Frailty models provide an essential tool for animal breeders who care about prediction of random variables, i.e. breeding values. But for this prediction it is need to know some parameters regarding the distribution of the frailty terms, in particular would be needed to know its variance.

Estimates of components of variance (additive genetic variance) and genetic parameters (heritability) of longevity are important issues in order to evaluate the possibility of including the trait in the selection programs as additional selection criterion beside the other productive or reproductive traits in rabbits.

For any trait estimates of heritability might differ between the studies depending on many factors: population under study, definition of the trait, model for the estimation and method of analysis. But for the case of longevity it is also needed to consider the scale of the reported heritability. Given the nonlinearity nature of the models used in the survival analysis for studying longevity records it is no obvious what is the adequate definition of the heritability, and this results in the existence of various forms to present this parameter. One interesting definition of heritability, related to the computation of the accuracy of breeding values estimates is the "effective heritability" which is computed as $h^2_e = \sigma^2_A / \sigma^2_A + 1$.

Other methods have been used to analyse longevity data, particularly for rabbit. These methods differ on the rigour of their approach and we can comment examples such as (1) Mixed linear models without taking into account the censored data. **Youssef at al. (2000)** estimated heritabilities for lifetime production and cumulative production traits of rabbits. They found that the estimates of heritability of the lifetime production traits ranged from 0.05 to 0.13. Another work in which linear models without censoring were used **(Lukefahr** and **Hamilton, 2000)** involved several genetic groups of rabbits that were compared for cumulative traits over one year and for survival throughout this period. (2) Repeated binary records, depending on if an animal is either still alive and remains in the breeding herd or is not (0 or 1) at different time periods defined by the users (day, week, month, year, etc.). In this case it has been shown that repeatability or random regression models can be used to estimate breeding values **(Meuwissen et al., 2002; Veerkamp et al., 1999)**. (3) Bayesian methodology and linear models with censoring for the analysis of longevity and prolificacy data in Landrace pigs **(Guo et al., 2001; Arango et al., 2005)**.

1.4. Genetic variability of longevity in rabbits.

One of the objectives of any program of selection in rabbits is to offer highly productive maternal does to the breeders and in the same time these does should have lower hazard of culling or mortality and, consequently, high lifetime production that mean resistance against diseases and low replacement rates. In this respect different genetic groups seem to have different longevities and productive potentialities and in this way encourage the comparison between breeds and lines of rabbits to know the differences in longevity and other productive traits.

Relevant differences in direct genetic effects for functional longevity defined as the ability to delay involuntary culling were found between maternal lines of rabbits highly selected for litter size at weaning **(Piles et al., 2006b). Lukefahr** and **Hamilton (2000)** in a longevity study to compare different genetic types concerned New Zealand White, Californian, and crosses between these two breeds, reported the superiority of the New Zealand White and crossbred does with respect to the Californian does. In the other hand, **Piles et al. (2006a)** in a study to assess doe longevity in two different lines of rabbits, found that results obtained in Prat and A1077 lines were quite similar despite differences in breeding schemes, voluntary culling rules, definition of reproductive longevity and modeling of the baseline hazard function. **Piles et al. (2006b)** in an diallel cross that involved three maternal lines of rabbits, A, V, and Prat, noticed that a purebred A doe was twice as likely to be replaced as a crossbred Prat x A doe and as a general pattern, the genetic type with the lowest relative risk were those in which the Prat line was involved; those were followed by types involving the V line and finally by those in which the line A participated. Another work involving Spanish maternal lines of rabbits is by **Sánchez et al. (2008)**. This is an experiment conducted to compare the performance of the new LP line with that of another well-known and well-performing, the line V, and to determine whether this new line could be considered as a candidate maternal line for inclusion in the current 3-way crossing production scheme. They reported that LP line have better longevity (better survival ability) especially later in life (fourth cycle) while V line have better early prolificacy and demonstrated that, if both lines were compared during the whole studied period, a log-hazard of -0.28 was detected which can be considered as significant for type I error (0.1), in favor of line LP.

The knowledge of doe rabbit longevity is important and as shown in the introduction, the studies analyzing differences in longevity among different lines of farm animals especially rabbits are actually scarce.

Regarding variability within population a number of studies reporting genetic variability and heritability has been published, table 2 summarizes their results.

Table (2) Estimates of variance components and heritability of doe rabbit longevity as cited from the literature.

Author and year	Breed or line	σ^2_S	σ^2_A	h^2	Method
Youssef et al. (2000)	NZW	0.224	-	0.13	Linear model without censoring
Garreau et al. (2001)	A1077 line	0.013		0.05	Weibull model, discrete variable
Garreau et al. (2001)	A1077 line	0.026		0.10	Weibull model, continous variable
Garreau et al. (2001)	A1077 line	0.063		0.24	Weibull model, unrelated sires
Sánchez et al. (2004a)	V-line	0.022	-	0.053	Survival analysis(Cox model)
Sánchez et al. (2006)	V-line	-	0.1811	0.099	Cox model
***Piles et al. (2006a)**	Prat line	-	0.1879	0.158	Cox model
***Piles et al. (2006a)**	Prat line	-	0.3116	0.237	Cox model
***Piles et al. (2006a)**	A1077 line	-	0.2072	0.172	Cox model
***Piles et al. (2006a)**	A1077 line	-	0.2299	0.187	Cox model

* In this work there were different models for that there were various estimates of variance components and different heritabilities; σ^2_S = sire variance; σ^2_A = additive genetic variance.

From these studies it could be concluded that in general the estimates of heritability of longevity are low. This fact, as well as the long time needed for recording relevant information, that only will be obtained in females, seems to prevent including this trait as a selection objective in traditional rabbit programs under low selection intensities.

1.5. Selection for longevity in rabbits.

So far a relative high number of studies dealing with genetics of rabbit does has been published, and most of them has been developed within the framework of projects with the final aim of performing selection experiments to improve doe longevity. In one hand the animal science department of the UPV created a new line, named L-P (Long-lived and Productive) **(Sánchez, 2005 and Sánchez et al., 2008)** this line was founded following a scheme similar to that applied in the selection for hyper-prolificacy in rabbits or pigs. In this case the selection criteria were hyper-longevity, selecting does in commercial farms which showed an extremely high productive life (does had at least 25 parities), and an average life prolificacy equal or above the population average (does were need to have at least 7 kits on average).

At INRA (France) a population was selected for longevity **(Garreau, et al. 2008)**, using exclusively within line information, in this case the selection criterion was the number of AIs a female was subject to during its entire life, and only males were selected according to this criteria, females was randomly selected.

Both approaches can be said to be successful for genetic improvement of longevity. The UPV´s L-P line was compared to another maternal line (V) and it showed a slightly better longevity, and slightly lower prolificacy, considering both traits, no differences in cumulative production was observed, the same as in fertility. Regarding the selection experiment in France, also better longevity was observed in the selected population (0.8 parturitions more) with an almost null effect on prolificacy.

In this two populations further studies has been conducted to assess the physiological basis of the longevity, and apparently the management of body reserves is a key issue for establishing their better longevity, particularly under unfavourable environmental conditions **(**L-P line**: Theilgaard et al. (2007);** INRA line**: Garreau et al., (2010))**.

2. OBJECTIVES

2. OBJECTIVES

The principal objective of this study is the comparison of longevity trait of four maternal lines of rabbits (A, V, H and LP) selected for litter size at weaning but founded on different criteria using the complete pedigree file and the complete data set performed from their foundation until March, 2011, and to realize this objective we have been done the consecutively steps:

A- Estimate the additive genetic variance of longevity, calculating the effective and equivalent heritabilities.

B- Estimate the differences for the longevity between the four lines at their foundation.

The second objective is phenotypically compare the lines at different moments of their selection program. These periods are from March 1997 to September 1998 for lines A, V and H, and from September 2009 to March 2011 for lines A, V and LP.

Finally it will be checked whether the observed phenotypically differences can be predicted from the differences at foundation and averages of estimated breeding values in the different set of comparison.

3.MATERIALS AND METHODS

3. MATERIALS AND METHODS

3.1. Housing and Management

Data used in the present study were collected from four Spanish maternal lines of rabbits (A, V, H, LP) reared in the closed nucleus of selection located in the farm of the Department of Animal Science, Polytechnic University of Valencia. Except the Line H, that was housed at the same farm until May, 2004 (10th generation of selection) when it was transferred to another nucleus of selection located in San Carlos de la Rápita (Tarragona), 180 Km north of Valencia.

Matings were carried out at random within lines but always taking care to avoiding that the mates had common grandparents. Age of bucks and does at the first mating ranged from 17 to 18 weeks. Using natural mating and in the early morning each doe was transferred to the assigned buck to be mated and returned back again to her own cage. On the day 12 post mating, each doe was palpated to detect pregnancy. Does not pregnant return to the same buck or another one to be remated and returned every other week until a service was observed. Likewise, does were remated 11 days after kindling by its assigned buck (semi-intensive system of production). On the 27th days of pregnancy, the nest boxes were supplied with thick wool, which was placed in the bottom of the nest box to help the doe in preparing a worm comfortable nest for her bunnies. Litters born were examined and recorded for LSB (total litter size at birth) and NBA (number born alive). Litters were checked and examined each morning during the suckling period to remove the dead bunnies. Without fostering, bunnies were reared by their mothers and weaned at 28 days post kindling, identified individually by a number tattooed on the left ear and transferred to standard progeny wire cages. Breeding animals and progeny were fed *ad libitum* on a pelleted commercial ration.

Culled does or dead ones were replaced by their substitutes from the same generation (from the same origin in the case of culled or dead bucks). The selection was in non overlapping generations and the does for the next generations were selected from the best evaluated matings. The bucks were selected within sires from the best matings trying that each sire contributed with a son to the next generation. Date and reason of the culling or death were recorded. For a suitable genetic evaluation of animals in the nucleus, common culling criteria in commercial farms are not considered; i.e. does with low levels of production or no strong reproductive delay, are not culled. In addition to the common practice of culling due to evident pathological problems (snuffles, sore hocks, mastitis, diarrhea, etc), does with three consecutive non fertile matings or with six consecutive refusals to the buck were culled. Also, the does that after two consecutive pregnancies did not have any young alive at weaning were also culled. All of the anterior reasons of culling are considered indicators of abnormal reproductive troubles but not indicators of poor production of healthy animals.

3.2. Animals

The four maternal lines were founded on different criteria but all selected for the same criterion (litter size at weaning).

3.2.1. Line A

The process of foundation began in 1976 sampling NZW rabbits, reared by farmers near Valencia (Spain). After three generations without selection, the line has been selected since 1980 by a family index (**Estany et al., 1989**) to increase litter size at weaning. The line is kept closed since its foundation.

3.2.2. Line V

Was founded in 1980 as a synthetic line, crossing animals that were progeny of four specialized maternal lines. After three generations without selection, the line has been selected (**Estany et al., 1989**) to increase litter size at weaning since 1982. The method of evaluating the animals is a BLUP under an animal- repeatability model. The line is kept closed since its foundation.

3.2.3. Line H

Was founded applying hyperprolific selection and embryo cryopreservation techniques (**García-Ximénez et al., 1996** and **Cifre et al., (1998)**. Hyperprolific does were assembled from a large commercial population, spread over different Spanish farms. The selection criterion was to improve litter size at weaning. The data used of this line were from the 1st generation (1997) to the 10th generation of selection (2004) obtained in the farm of the UPV. The data from the 11th to the 18th generation, obtained in the farm of San Carlos de la Rápita, were not used in the study.

3.2.4. Line LP

Was founded by selecting females from commercial farms that showed extremely high productive lives (measured as the number of parities) with prolificacy (measured as the mean number of born alive per parity) near or above the average of the Spanish commercial rabbit populations (**Sánchez, 2005 and Sánchez et al., 2008**). This line, now, is selected for litter size at weaning, since 2003.

Table (3): Differences between the four Spanish maternal lines of rabbits used in the present study.

Line	Origin of the line	Criterion of selection	Method of selection	Recent generation of selection	Reference
A	NZW	LSW	Family Index	41	**Estany et al. (1989)**
V	Four maternal lines	LSW	Blup under repeatability animal model	37	**Estany et al. (1989)**
H	Hyperprolific commercial does	LSW	Blup under repeatability animal model	18	**Cifre et al. (1998)**
LP	Hyper long-lived commercial does	LSW	Blup under repeatability animal model	7	**Sánchez (2005) and Sánchez et al. (2008)**

* LSW = Litter size at weaning; NZW = New Zealand White; number of bucks per generation for each lines was around 25; number of does per generation for each line was around 125.

3.3. Data

Records for this study were collected during the program of selection of maternal lines of rabbits from September 1980 to March 2011 in a closed nucleus of selection located in the farm of the Department of Animal Science, Polytechnic University of Valencia (UPV). The data of line H obtained in San Carlos de la Rápita were not considered. The complete data set included the reproductive records of all generations of selection of all lines involving 12693 does. The complete pedigree file had 14805 records. The uncensored data form about 59.57 % of whole data. The individual records of each animal included the date of the first positive pregnancy test and the date of death, culling or censoring. The difference between these dates and censoring code (0=alive; 1=death) were the response variables.

Table(4): Minimum, maximum and average productive life for censored and uncensored records in the data set (Complete data set from the foundation until March 2011, lines A, V, H and LP).

	Censored[a] Records 5132 (40.43%)	Uncensored[b] Records 7561 (59.57%)
Minimum time (d)	3	3
Maximum time (d)	922	819
Average time (d)	270.86	173.35

[a]Records from does that had not completed their productive life.

[b]Records from does that had completed their productive life.

* Total number of elementary records: 237907.

This analysis was performed to compare the four lines at the moment of their foundation using data recorded during the common year-seasons between each two lines which were from September 1982 to September 2003 and from March 2006 to March 2011for lines A and V, from March 1997 to September 1998 for lines A and H, from March 2006 to March 2011 for lines A and LP, from March 1997 to September 1998 for lines V and H; and from September 2004 to March 2011 for lines V and LP. The lines H and LP only had one year-season in common because the line LP was founded at 2003 while line H was transferred at May 2004 to another nucleus of selection in San Carlos de la Rápita (Tarragona) where the management and environmental conditions are different. Survival analysis was performed using the program of Survival Kit 6.0 (**Ducrocq et al., 2010**), this software implements the survival analysis methodology (**Ducrocq** and **Casella, 1996**) and the model of analysis was the Cox proportional hazard model. The analysis was performed to compare the three lines A, V, and H at fixed time using data recorded during the common year-seasons shared by the three lines which were from March 1997 to September 1998.

Table (5): Minimum, maximum and average productive life for censored and uncensored records in the data set (Records from March 1997 to September 1998, lines A, V, and H).

	Censored[a] Records 493 (45.06%)	Uncensored[b] Records 601 (54.94%)
Minimum time (d)	42	31
Maximum time (d)	424	347
Average time (d)	220.44	155.51

[a]Records from does that had not completed their productive life.

[b]Records from does that had completed their productive life.

* Total number of elementary records: 17000.

The analysis was performed to compare the three lines A, V, and LP at fixed time using data recorded during the common year-seasons shared by the three lines which were from September 2009 to March 2011.

Table (6): Minimum, maximum and average productive life for censored and uncensored records in the data set (Records form September 2009 to March 2011, lines A, V, and LP).

	Censored[a] Records 643 (66.29%)	Uncensored[b] Records 327 (33.71%)
Minimum time (d)	35	3
Maximum time (d)	661	487
Average time (d)	263.89	168.34

* [a]Records from does that had not completed their productive life.

[b]Records from does that had completed their productive life.

* Total number of elementary records: 20013.

3.4. Statistical models

The complete genetic model proposed was the following frailty model:

$h_i(t|\mathbf{x}'_i(t)) = h_0(t)*\exp\{\mathbf{x}_i'(t)_{LYS}\,\boldsymbol{\beta}_{LYS} + \mathbf{x}_i'(t)_{PS}\,\boldsymbol{\beta}_{PS} + \mathbf{x}_i'(t)_{OPP}\,\boldsymbol{\beta}_{OPP} + \mathbf{x}_i'(t)_{BA}\,\boldsymbol{\beta}_{BA} + \mathbf{z}_i'\mathbf{u}\}$

Where the anterior terms are:

$h_i(t|\mathbf{x}'_i(t))$ is the hazard of animal i at time t, affected by covariates indicated by $\mathbf{x}_i'(t) = \{\mathbf{x}_i'(t)_{LYS}, \mathbf{x}_i'(t)_{PS}, \mathbf{x}_i'(t)_{OPP}, \mathbf{x}_i'(t)_{BA}, \mathbf{z}_i'\}$; $h_0(t)$ is the baseline hazard at time t (in the Cox model is not defined by any function); $\mathbf{x}_i(t)_{LYS}$ is the vector which selects the levels of line-year-season combination (LYS) which at time t is affecting the animal i; $\mathbf{x}_i(t)_{PS}$ is the vector which selects the levels of physiological status (PS) of the doe at the time of mating (pregnant, lactating, non-pregnant, and pregnant&lactating) which at time t is affecting the animal i; $\mathbf{x}_i(t)_{OPP}$ is the vector which selects the levels of the order of the positive palpation (OPP) which at time t is affecting the animal i and this factor was categorized into 6 levels; $\mathbf{x}_i(t)_{BA}$ is the vector which selects the levels of number born alive (BA) of the doe which at time t is affecting the animal i. In order to have a sufficient number of observations for each level of number born alive this factor was categorized into 9 levels, the first one included nulliparous does, the second level included does that had zero born alive, the third one included does that had 1 or 2 born alive, and so on until the ninth level which included does had more than or equal 13 born alive, and finally $\mathbf{u}$ is the vector of additive genetic values, assumed random, and with the variance-covariance structure defined by the additive relationship matrix, $\mathbf{z}$ is the vector that selects the animal effect in $\mathbf{u}$.

For the comparison between lines at fixed times, a second model was used in this case a fixed model having the fixed and time dependent factors that affect the risk during the life of does without including the additive genetic effect of the animal.

The existence of a high proportion of does dying in the first parturition makes the data to misfit the Weibull model, for this reason it is recommended to choose the semiparametric approach of the Cox model **(Sánchez et al., 2004a; Piles et al., 2006a)**.

3.4.1. Estimation of additive genetic variance and heritability

The analysis using the previous complete genetic model was performed to estimate the genetic variance for the longevity trait (length of productive life, LPL) and then the effective heritability was calculated as $h^2 = \sigma^2_A / \sigma^2_A + 1$. This formula corresponds to the extension to the Cox and discrete survival animal models of the formula of **Yazdi et al. (2002)** developed for a Weibull sire model. This extension was validated for the Cox model through simulation by J. P. Sánchez (personal communication, Universidad Politécnica de Valencia, Spain). The effective heritability is a heritability referred to the original scale. It is the one that can be used to compute approximate reliabilities or expected genetic gains similar to the classical linear models. These heritability estimates are maximum values, considering that all records are uncensored, this means that increasing censoring rate decreases the heritability estimate. If the proportion of uncensored records until a given time is p, the value of h^2 such that the reliability can be computed using the index of selection formula (equivalent heritability), is given by the expression $h^2_{equi} = \sigma^2_A / \sigma^2_A + (1/p)$ **(Yazdi et al., 2002)**.

3.4.2. Comparison between lines at foundation times

Using the variance components estimated in the previous step, the fixed of the complete model and data set were estimated. Through the additive effects of the animals, the component line of the factor line-year-season refers to the foundation time of the lines. Thus, the contrast of the differences between each pair of lines at foundation is computed as the difference of the averages, for each line, of the line-year-season effects corresponding to the year-seasons common to both lines.

3.4.3. Observed and Expected differences between lines at fixed times

Additive genetic effects were excluded from the model and only the data recorded during the shared year-seasons of comparison were used, thus the line effects refer to the real genetic merit of these lines at the time of comparison as a consequence of selection and genetic drift but not being dependent on the genetic model. The differences between two lines at the defined periods will be computed as the differences between the averages for each line of the line-year-season effects of the period.

The solutions of the complete model and data set will be used to compute the expected differences between lines at a given time period shared between them. The predicted contrast between two lines will be computed in the same way as it has been explained in the section 3.3.2 but limited to the year-seasons contributed in the different period, and to this quantity the additive values of the animals performing during that period will be added. This will be done summing to the different lines the difference between lines the averages of the predicted breeding value of animals living during that period.

Thus the observed differences will be compared with the expected ones as a way to check the adequacy of the complete model to predict breeding values and to estimate differences between lines.

4.RESULTS AND DISCUSSION

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4.1. Genetic aspects (heritability of longevity).

The result from the complete genetic model gave an estimate of additive genetic variance of 0.195 and standard deviation of 0.03 which corresponds to a effective heritability of 0.163, and this estimate of heritability is considered as an average of heritabilities of the four lines involved in this analysis, because the data used is composed of all data obtained from these four lines which reared in a closed nucleus of selection. Make allowances for the proportion of uncensored records (p) which was 59.57 % of all records and using the resulted additive genetic variance of 0.195 these values leads to an estimate of equivalent heritability of 0.104. The estimate of effective heritability in the present study is larger than the one previously reported by **Sánchez et al. (2004)** (0.053). These two values should be compared with caution since here the trait definition is different, the physiological state is defined in a different way, the population of rabbits is different, and in the present study we used an animal model but **Sánchez et al. (2004)** used a sire-maternal grandsire model. Other estimates of the heritability for longevity were reported by **Garreau et al. (2001)**, who studied this parameter using different models, and the estimated value under the most realistic model was 0.05. An estimate of heritability using a Bayesian methodology and the Cox animal model was of **Sánchez et al. (2006)** who reported an additive genetic variance of 0.181 (posterior mean) which corresponds to a heritability of 0.099 on the $\log(g(t_i))$ scale. This figure is defined on a different scale but is still a low value. Our estimate of heritability is within the range of the different estimates of heritability reported by **Piles et al., (2006a)** (0.158 to 0.237).

4.2. Comparison between A, V, H and LP lines at their foundation.

The comparison among lines at their foundation is shown in Table (7).The lines V, H and LP showed a significant superiority over line A. The greatest difference was between the lines A and LP. We can note that the line

LP was created using does that had at least 25 parities as indicator of hyper-longevity and the longer productive life of LP females could partially be understood as an indicator of success of the selection procedure during the foundation of this line. In the other hand the line A was created by mating does and bucks of the New Zealand White breed belonged to commercial populations that primarily maintained the standard characteristics of the breed. We can not forget to cite that the line A had the higher susceptibility to enterocolitis disease which was present during some periods shared with the other lines. **Piles et al. (2006b)** found relevant differences in direct genetic effects for functional longevity between maternal lines A, V and Prat selected for litter size at weaning. However **Sánchez et al. (2008)** indicated the superiority of the line LP over the line V in the survival ability, especially at later cycles and commented that this could be expected, because the selection procedure in the LP line was focused on late survival. The lines H and LP only had one year-season in common and for this reason the comparison between both has not been carried out. The relative risk describes how much more likely it is that culling or death occurs within one level of a given factor relative to another level of the same factor. For example in table 7 an A animal culling or dying is 3.4 times more likely than a V animal.

Table (7): Contrasts between the lines A,V,H and LP for the longevity trait shows the estimated values and relative risk as resulted from the survival analysis performed at the foundation time of these lines.

Contrast	Estimate	SE	Relative risk	X^2	*P-value*
A *vs* V	1.223^*	0.259	3.40	22.32	0.00
A *vs* H	1.232^*	0.287	3.43	18.41	0.00
A *vs* LP	1.716^*	0.327	5.56	27.53	0.00
V *vs* H	-0.291	0.267	0.75	1.19	0.276
V *vs* LP	0.003	0.289	1.00	0.00	0.991

* SE : Standard error; X^2 : Chi-Square.

4.3. Comparison between lines at fixed times.

The observed differences between the three maternal lines A, V and H from March 1997 to September 1998 are presented in Table (8). It is shown that line A had a risk of death or culling greater than lines V and H, the same trend as in the case of the comparison at the foundation time of these lines.

Table (8): Contrasts between the lines A,V and H for the longevity trait shows the estimated, relative risk as resulted from the survival analysis performed using data from March 1997 to September 1998.

Contrast	Estimate	SE	Relative risk	X^2	*P-value*
A *vs* V	0.347^*	0.101	1.42	11.77	0.00
A *vs* H	0.278^*	0.111	1.32	6.29	0.012
V *vs* H	-0.069	0.106	0.93	0.43	0.513

* SE : Standard error; X^2 : Chi-Square.

The expected values of the differences of the hazard between lines were 0.41, 0.22 and -0.18 for the contrasts between A *vs* V; A *vs* H; and V *vs* H lines respectively, showing that the observed and expected values of the hazard are relatively similar. This means that the complete model used in the analysis was suitable to describe this longevity data.

The observed differences between the three maternal lines A, V and LP from September 2009 to March 2011 are presented in Table (9). The comparisons reflect the current situation of the three lines. The contrasts show the inferiority of the line A over the two other lines, as the comparison at foundation. The limited capacity of the line A to face the opposite risk factors in comparison with the other three lines means lower longevity of this line and this finding is in agreement with those of **Ragab et al. (2011)** who demonstrated that lines A and line H have a similar ability to avoid risk factors and both of them are more sensitive to these factors than lines V and LP. No significant differences between the V and LP lines has been found, contrarily to the result of **Sánchez et al. 2008** who found that the LP line had a longer reproductive life than the V line.

Table (9): Contrasts between the lines A,V and LP for the longevity trait shows the estimated values and relative risk as resulted from the survival analysis performed using data from September 2009 to March 2011.

Contrast	**Estimate**	**SE**	**Relative risk**	**X^2**	***P-value***
A *vs* V	0.347^*	0.141	1.41	6.02	0.014
A *vs* LP	0.539^*	0.148	1.71	13.31	0.00
V *vs* LP	0.192	0.149	1.21	1.66	0.198

* SE : Standard error; X^2 : Chi-Square.

The expected values of the differences of the hazard between lines, computed from the analysis of the complete model and data set, were 0.36, 0.54 and 0.18 for the contrasts between A *vs* V; A *vs* LP; and V *vs* LP lines respectively, showing that the observed and expected values of the hazard differences are relatively similar, indicating again the suitability of the complete model.

The observed differences between lines during these periods are lower than those at the moment of their foundation. This result may be due to a positive correlation between the prolificacy and longevity means improvement in the longevity of these lines as a consequence of the improvement of prolificacy traits resulted from selection process which makes lines increasingly similar.

4.4. Time dependent factors estimates.

Only the order of the positive palpation (OPP), the physiological status of the doe (PS); and number born alive (BA) will be considered.

4.4.1. Order of the positive palpation (OPP).

The effects of the order of positive palpation (OPP), for females having at least one parturition, are presented in Table (10) (thus we start in the level 2, which the first positive palpation after the parturition). It is clear that as the order of positive palpation increases after the 2nd positive palpation the risk ratio decreases, showing that older does were capable to face the parity as a risk factor better than the young ones. This result could be expected if it is considered that the young does become pregnant and lactating when they are still growing, fact that increases the risk. This result is in agreement with those of **Sánchez et al. (2004, 2006),** who found that the animals at the firsts order of positive pregnancy test always had the highest risk.

Table (10): Estimates of the hazard, standard error, relative risk and number of uncensored data for each level of the order of positive palpation, (OPP).

OPP	Estimate	SE	X^2	P-Value	Risk Ratio	Uncensored Failures
2	1.909	0.109	309.55	0.000	6.752	1327
3	1.245	0.082	228.20	0.000	3.473	1684
4	0.819	0.065	159.28	0.000	2.270	1523
5	0.436	0.051	71.70	0.000	1.546	1202
6	0.000	-	-	-	1.000	1776

4.4.2. Physiological status of the doe (PS).

The effects of doe physiological status, as a time dependent factor affecting longevity of the doe, are presented in Table (11). As shown in the table, non-pregnant does had the greatest risk of culling (with respect to the last level); this can be expected if the failure to conceive is considered as an indicator of disease. These findings are in agreement with those of **Sánchez et al. (2006)** who found that the physiological state “Empty” was always the level with the highest relative risk followed by “Pregnant”, “Lactating” and finally “Pregnant & Lactating”.

Table (11) Estimates of the hazard, standard error, relative risk and number of uncensored data for each level of physiological status, (PS).

Status	Estimate	SE	X^2	P-Value	Risk Ratio	Uncensored Failures
Pregnant	-1.176	0.036	1048.54	0.000	0.308	1691
Lactating	-0.963	0.042	526.21	0.000	0.382	1845
pregnant & lactating	-0.891	0.038	550.03	0.000	0.410	1945
Non-pregnant	0.000	-	-	-	1.000	2080

4.4.3. Number born alive (BA).

The effects of the number of bunnies born alive at each kindling are presented in Table (12). As the number of born alive moves from zero to more than one the relative risk (with respect to the last level) become lower, between the other levels does not seen to exist differences in risk. This pattern is in agreement with those of **Garreau et al. (2001), Sánchez et al. (2004)** and **Piles et al. (2006a**). In our data set there was no culling for productive reasons, this is a need for the right evaluation of the animals for prolificacy during the selection process, so very low levels of BA would be indicators of sick does and underlying pathological problems, because they had the highest relative risks. Longevity does not seem to be unfavourably influenced by large litter size. Similarly increasing litter size in our lines under study by selection did not increase culling rate, these findings are in agreement with those of **Tudela et al. (2003)** and **Piles et al. (2006a**). The fact, that for the number of born alive higher than zero, the risk does not change, is compatible with a very low genetic correlation between longevity and litter size this fact is in agreement with those of **Sánchez et al. (2004b)**.

Table (12): Estimates of the hazard, standard error, relative risk and number of uncensored data for each level of number born alive, (BA).

Level	Estimate	SE	X^2	P-Value	Risk Ratio	Uncensored Failures
Does had Zero BA	0.907	0.059	231.52	0.000	2.476	563
Does had 1 or 2 BA	0.074	0.083	0.80	0.370	1.077	193
Does had 3 or 4 BA	0.092	0.065	2.02	0.155	1.097	384
Does had 5 or 6 BA	-0.015	0.054	0.07	0.787	0.985	720
Does had 7 or 8 BA	0.000	0.047	0.00	0.999	1.000	1402
Does had 9 or 10 BA	-0.035	0.044	0.63	0.426	0.966	1833
Does had 11 or 12 BA	-0.099	0.044	4.92	0.027	0.906	1444
Does had ≥ 13 BA	0.000	-	-	-	1.000	857

5.CONCLUSIONS

5. CONCLUSIONS

1- The estimated additive genetic variance of longevity was 0.195.This estimate corresponds to an effective heritability of 0.163, while corresponds to an equivalent heritability of 0.104 considering the proportion of uncensored data as 59.57 %.

2- Lines V, H and LP showed a significant superiority over line A at their foundation. The greatest difference was between the lines A and LP, while the differences between line V and both of H and LP lines were small and non significant. These differences between lines may be attributed to the history of foundation of each line where all of them were founded on different criteria.

3- Both during the period from March, 1997 to September, 1998 and from September, 2009 to March, 2011, it is shown that line A had a risk of culling or death greater than lines V, H and LP. This means that apparently line A has limited capacity to face the opposite risk factors. No significant differences between V and LP and between V and H lines has been founded.

4- The observed current differences between lines were lower than those observed at the foundation time, this result may be due to a positive correlation between prolificacy and longevity, and thus a selection process will makes lines increasingly similar on longevity.

5- The expected differences between lines at the two fixed times computed using the complete genetic model match well the current phenotypic differences between lines. This means that the complete model is suitable to describe this longevity data set, for predicting breeding values and estimating genetic differences between lines.