Bone 109 (2018) 124–133

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Joint-specific risk of impaired function in fibrodysplasia ossificans progressiva (FOP)

Robert J. Pignolo [a,*,1,2], Blythe P. Durbin-Johnson [b,1,3], David M. Rocke [b,4], Frederick S. Kaplan [c,d,e,5]

[a] Department of Medicine, Mayo Clinic School of Medicine, Mayo Clinic, Rochester, MN, United States
[b] Department of Public Health Sciences, School of Medicine, Department of Biomedical Engineering, University of California, Davis, CA, United States
[c] Department of Orthopaedic Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States
[d] Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States
[e] The Center for Research in FOP and Related Disorders, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

ARTICLE INFO

Article history:
Received 27 April 2017
Revised 10 June 2017
Accepted 11 June 2017
Available online 13 June 2017

Keywords:
Fibrodysplasia ossificans progressiva
Heterotopic ossification
Bone morphogenetic protein signaling
ACVR1
Joint survival
Risk

ABSTRACT

Background: Fibrodysplasia ossificans progressiva (FOP) causes progressive disability due to heterotopic ossification from episodic flare-ups. Using data from 500 FOP patients (representing 63% of all known patients worldwide), age- and joint-specific risks of new joint involvement were estimated using parametric and nonparametric statistical methods.

Results: Compared to data from a 1994 survey of 44 individuals with FOP, our current estimates of age- and joint-specific risks of new joint involvement are more accurate (narrower confidence limits), based on a wider range of ages, and have less bias due to its greater comprehensiveness (captures over three-fifths of the known FOP patients worldwide). For the neck, chest, abdomen, and upper back, the estimated hazard decreases over time. For the jaw, lower back, shoulder, elbow, wrist, fingers, hip, knee, ankle, and foot, the estimated hazard increases initially then either plateaus or decreases. At any given time and for any anatomic site, the data indicate which joints are at risk.

Conclusions: This study of approximately 63% of the world's known population of FOP patients provides a refined estimate of risk for new involvement at any joint at any age, as well as the proportion of patients with uninvolved joints at any age. Importantly, these joint-specific survival curves can be used to facilitate clinical trial design and to determine if potential treatments can modify the predicted trajectory of progressive joint dysfunction.

© 2017 Elsevier Inc. All rights reserved.

1. Introduction

Fibrodysplasia ossificans progressiva (FOP; OMIM: 135100) is an ultra-rare, progressively disabling genetic disorder characterized by congenital malformation of the great toes and by progressive heterotopic ossification (HO) through an endochrondal process [1–5]. Progressive HO begins during the first decade of life and becomes more widespread throughout life [2–4,6,7]. Impending ossification at a site is often preceded by painful areas of inflammatory fibroproliferative flare-ups involving tendons, ligaments, and connective tissue of skeletal muscle that rigidly immobilize the joints of the axial and appendicular skeleton [3,4,6].

HO can be incited by blunt trauma, surgery, intramuscular injections (especially vaccinations), viral illness, or muscular overuse, but most often occurs spontaneously. There is a clear immunological, inflammatory, and/or hypoxic component that contributes to early lesion development [8–10]. Diaphragm, tongue, extraocular, facial, cardiac and smooth muscle are characteristically spared [11]. Early death results most often from respiratory failure caused by restrictive disease of the chest wall [12].

In 1994, Rocke et al. used data from a survey of 44 FOP patients to estimate age- and joint-specific risk of new joint involvement as a clinically useful guide to the patterns of progression of the disease [13]. In this study, global natural history data from 500 FOP patients, based on a

* Corresponding author.
E-mail addresses: pignolo.robert@mayo.edu (R.J. Pignolo), bpdurbin@ucdavis.edu (B.P. Durbin-Johnson), dmrocke@ucdavis.edu (D.M. Rocke), frederick.kaplan@uphs.upenn.edu (F.S. Kaplan).
[1] Equal contribution.
[2] Division of Geriatric Medicine & Gerontology, Robert and Arlene Kogod Professor of Geriatric Medicine, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905.
[3] Department of Public Health Sciences, Division of Biostatistics, University of California, Davis, One Shields Avenue, Davis, CA 95616.
[4] Department of Public Health Sciences, Division of Biostatistics, Med Sci 1C, Room 140B, University of California, Davis, One Shields Avenue, Davis, CA 95616.
[5] Isaac & Rose Nassau Professor of Orthopaedic Molecular Medicine, Division of Orthopaedic Molecular Medicine, Perelman School of Medicine, The University of Pennsylvania c/o Department of Orthopaedic Surgery, Penn Musculoskeletal Center - Suite 600, 3737 Market Street, Philadelphia, PA 19104.

http://dx.doi.org/10.1016/j.bone.2017.06.009
8756-3282/© 2017 Elsevier Inc. All rights reserved.

Table 1
Demographic and disease characteristics.

Current age (years)	
N	500
Mean (SD)	24.2 (14.1)
Median (range)	22.7 (1.2–71.4)
Age at diagnosis (years)	
N	498
Mean (SD)	6.9 (6.5)
Median (range)	5.0 (0–63)
Sex (n, %)	
Female	279 (55.8%)
Male	221 (44.2%)
Survey language (n, %)	
English	204 (40.8%)
Chinese	54 (10.8%)
Danish	2 (0.4%)
Dutch	10 (2%)
French	18 (3.6%)
German	24 (4.8%)
Italian	16 (3.2%)
Japanese	24 (4.8%)
Korean	25 (5%)
Polish	11 (2.2%)
Portuguese	42 (8.4%)
Serbian	5 (1%)
Spanish	53 (10.6%)
Swedish	12 (2.4%)
Areas affected (n, %)	
Any	479 (95.8%)
Jaw	242 (48.4%)
Neck	428 (85.6%)
Upper Back	399 (79.8%)
Lower Back	351 (70.2%)
Chest	252 (50.4%)
Abdomen	135 (27%)
Shoulder	401 (80.2%)
Elbow	304 (60.8%)
Wrist	158 (31.6%)
Fingers	89 (17.8%)
Hip	313 (62.6%)
Knee	267 (53.4%)
Ankle	205 (41%)
Foot	130 (26%)

comprehensive study by Pignolo et al. [14], was used to make more precise and clinically relevant estimates of the risk of HO by age and anatomic site. Such estimates of risk are valuable in helping individual patients and families plan for anticipated needs associated with progressive disability. These estimates of risk will aid in the design of clinical trials to estimate effects of chronic treatment and to evaluate therapies when randomized controlled trials are impractical because of the extreme rarity of the disease.

2. Methods

2.1. Patients

Data were analyzed from 500 FOP patients who completed a worldwide, prospective, cross-sectional survey of flare-ups, episodic exacerbations that over time result in disabling HO [14].

2.2. Data censoring

For central (axial) joints, the age at which a given joint was first affected was set to the age recorded in the survey plus 6 months, if the joint was indicated as affected and an age was given, and censored at the current age otherwise (i.e., the age at which a joint would be affected is not known except that it is at least the current age). For appendicular sites, if contralateral joints were affected, the earlier of the two ages plus 6 months was used as the age affected. If one of two contralateral joints was affected, that age was used as the age affected; if neither joint was affected, or if no age was given, the data were censored at the current age.

2.3. Data analysis

Survival functions for the age at which a given joint was affected were estimated using the Kaplan-Meier method [15] and median ages affected and other quantiles (i.e., 25th and 75th percentiles) were calculated from these survival functions. Confidence intervals for survival functions and quantiles were calculated using the method of Greenwood [16]. Hazard functions and associated confidence intervals were

Table 2
Summary of ages at which each joint is affected.

Area	Current data			1994 data		
	Median age affected (95% CI)	25th percentile (95% CI)	75th percentile (95% CI)	Median age affected (95% CI)	25th percentile (95% CI)	75th percentile (95% CI)
Jaw	23.5 (21.5, 25.5)	15.5 (14.5, 17.5)	40.5 (36.5, NR)	22.5 (20.5, 26.5)	15.5 (10.5, 21.08)	26.5 (25.25, NR)
Neck	8.5 (7.5, 9.5)	3.5 (3.5, 4.5)	16.5 (15.5, 20.5)	5.5 (3.5, 9.7)	2.5 (2.0, 4.0)	11.1 (9.5, 17.5)
Upper Back	9.5 (7.5, 10.5)	4.5 (3.5, 4.5)	18.5 (16.5, 30.5)	n/a	n/a	n/a
Lower Back	13.5 (12.5, 14.5)	5.5 (5.5, 6.5)	32.5 (23.5, NR)	n/a	n/a	n/a
Spine	n/a	n/a	n/a	5.8 (5.1, 10.5)	3.5 (2.5, 5.5)	11.5 (10.5, 18.5)
Chest	38.5 (30.5, NR)	11.5 (9.5, 12.5)	NR (NR, NR)	n/a	n/a	n/a
Abdomen	NR (NR, NR)	35.5 (26.5, NR)	NR (NR, NR)	n/a	n/a	n/a
Shoulder	11.5 (10.5, 12.5)	5.5 (4.5, 5.5)	20.5 (17.5, 27.5)	6.0 (5.5, 11.2)	3.5 (2.5, 5.5)	11.5 (10.5, 16.5)
Elbow	18.5 (17.5, 20.5)	10.5 (9.5, 12.5)	34.5 (30.5, NR)	16.5 (9.5, 26.5)	5.9 (3.5, 11.5)	27.5 (21.25, NR)
Wrist	54.5 (45.5, NR)	21.5 (19.5, 28.5)	NR (63.5, NR)	27.5 (23.5, NR)	20.5 (12.5, 25.3)	NR (NR, NR)
Fingers	NR (NR, NR)	50.5 (39.5, NR)	NR (NR, NR)	46.5 (NR, NR)	46.5 (NR, NR)	46.5 (NR, NR)
Hip	18.5 (16.5, 20.5)	12.5 (12.5, 13.5)	30.5 (27.5, 33.5)	14.4 (12.5, 17.5)	10.5 (6, 12.5)	19.5 (16.5, NR)
Knee	20.5 (19.5, 24.5)	13.5 (12.5, 15.5)	34.5 (30.5, NR)	17.5 (12.5, 27.5)	10.5 (10.5, 15)	27.5 (19.67, NR)
Ankle	33.5 (29.5, 40.5)	17.5 (16.5, 20.5)	NR (51.5, NR)	23.5 (18.5, NR)	17.5 (12.5, 20.5)	39.2 (36.5, NR)
Foot	58.5 (55.5, NR)	30.5 (25.5, 39.5)	NR (NR, NR)	n/a	n/a	n/a
Toes	n/a	n/a	n/a	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)

The left three columns show the median, 25th percentile, and 75th percentile of the age at which each joint surveyed is affected, and associated 95% confidence intervals, for the 2014 survey. The right three columns show the median, 25th percentile, and 75th percentile of the age at which each joint surveyed was affected, and associated 95% confidence intervals, for the 1994 data. "n/a" indicates that the survey did not inquire as to the status of that joint. NR indicates that an insufficient proportion of survey subjects had been affected at that area for the quantile or confidence bound to be calculated.

estimated using nonparametric smoothing as implemented in the R package bshazard [17].

The conditional probability of a patient having no additional joints affected in the next year, given his or her current status, was calculated as the product over all unaffected joints (j):

$$S_j(\text{current age} + 1)/S_j\ (\text{current age}),$$

where S_j is the Kaplan-Meier estimate of the joint-specific survival function.

Analyses were conducted using the statistical software environment R, version 3.1.2 [18].

The annualized risk for each joint at age t (defined as the conditional probability of an event by age $t + 1$, given that the joint has remained unaffected until age t), is defined as:

$$S_j(t+1)/S_j\ (t), \tag{1}$$

where S_j is the joint-specific survival function. Annualized risks were estimated by substituting the Kaplan-Meier estimate of the joint specific survival function for S_j in the above formula. 95% confidence intervals were constructed for $\ln[S_j(t+1)] - \ln[S_j(t)]$ based on the variance for the log of the Kaplan-Meier estimate given in Greenwood [16]; confidence interval endpoints were then transformed to give a confidence interval for the annualized risk.

3. Results

3.1. Demographics and disease characteristics

Table 1 summarizes demographic and disease characteristics of the 500 survey participants. The median age of participants was 23 years (range 1 years to 71 years), and 56% of participants were female. The median age at diagnosis was 5 years (range 0 years to 63 years). Forty-one percent of respondents completed an English language version of the survey; the next most common languages were Chinese (11%) and Spanish (11%).

3.2. Joint survival curves

All but 21 subjects reported at least one area affected; the areas most commonly affected were the neck (86%), shoulder (80%), upper back (80%), and lower back (70%).

Table 2 shows Kaplan-Meier estimates of quantiles of the age at which each area was affected, for the current survey and for a 1994 survey that included 44 participants with a median age of 27.5 years. Median ages for affected joints were older in the current survey sample, for all areas that were included in both surveys. In the current survey, the areas affected earliest were the neck (median age 8.5 years), the upper back (median age 9.5 years), and the shoulder (median age 11.5 years). The areas affected latest were the foot (median age 58.5 years) and fingers (median not reached, 25th percentile is 50.5 years). Kaplan-Meier curves of the age at which each joint was affected are shown for the upper extremity, excepting the fingers (Fig. 1), the axial skeleton (Fig. 2), and the lower extremity (Fig. 3). There was no significant difference by sex in the survival curve for any joint.

3.3. Joint-specific risk of involvement

The annualized risk of a joint being affected is defined as the conditional probability of an event in the next year, given that the joint has remained unaffected up to the indicated age. Table 3 shows the annualized risk for each joint over time, estimated from the Kaplan-Meier survival curve, and 95% confidence intervals.

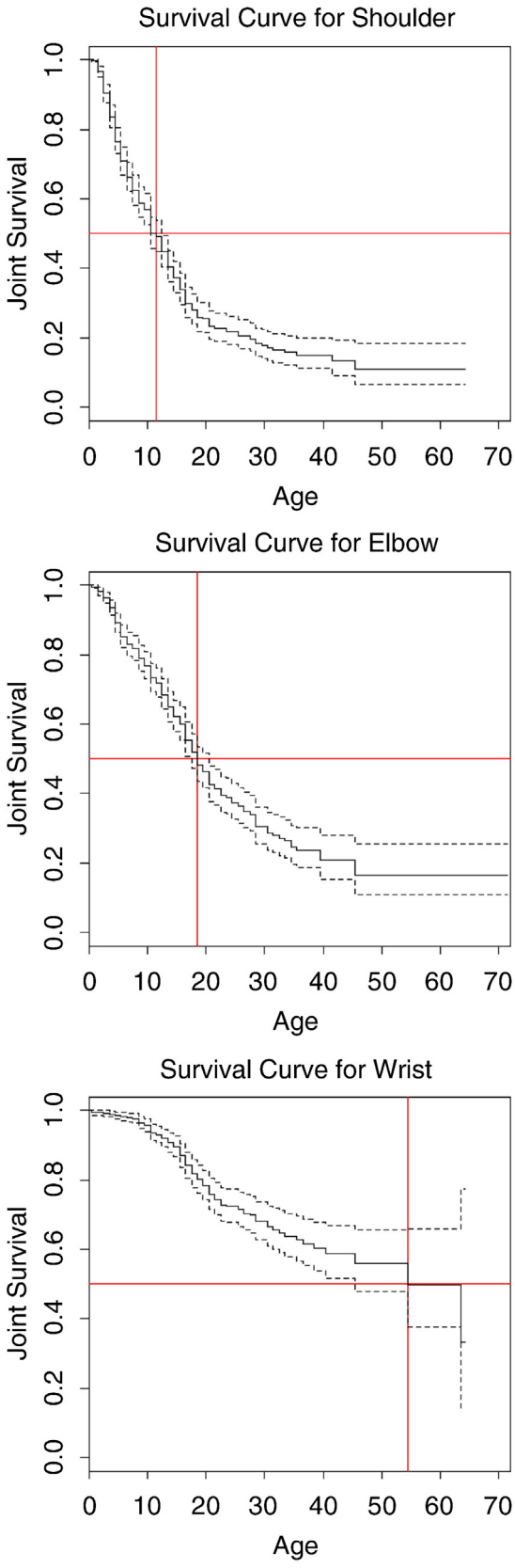

Fig. 1. Kaplan-Meier survival curves for the upper extremity. The y-axis shows estimated survival (the proportion of respondents with that joint unaffected as of that age), the x-axis shows age in years. The solid black line is the estimated survival and the dashed lines show 95% confidence intervals. The red line indicates 50% survival, the age at which the estimated survival curve crosses the red line (if applicable) is the median age at which the joint is first affected. The median age at which each joint is first affected is 11.5 years (shoulder), 18.5 years (elbow), and 54.5 years (wrist).

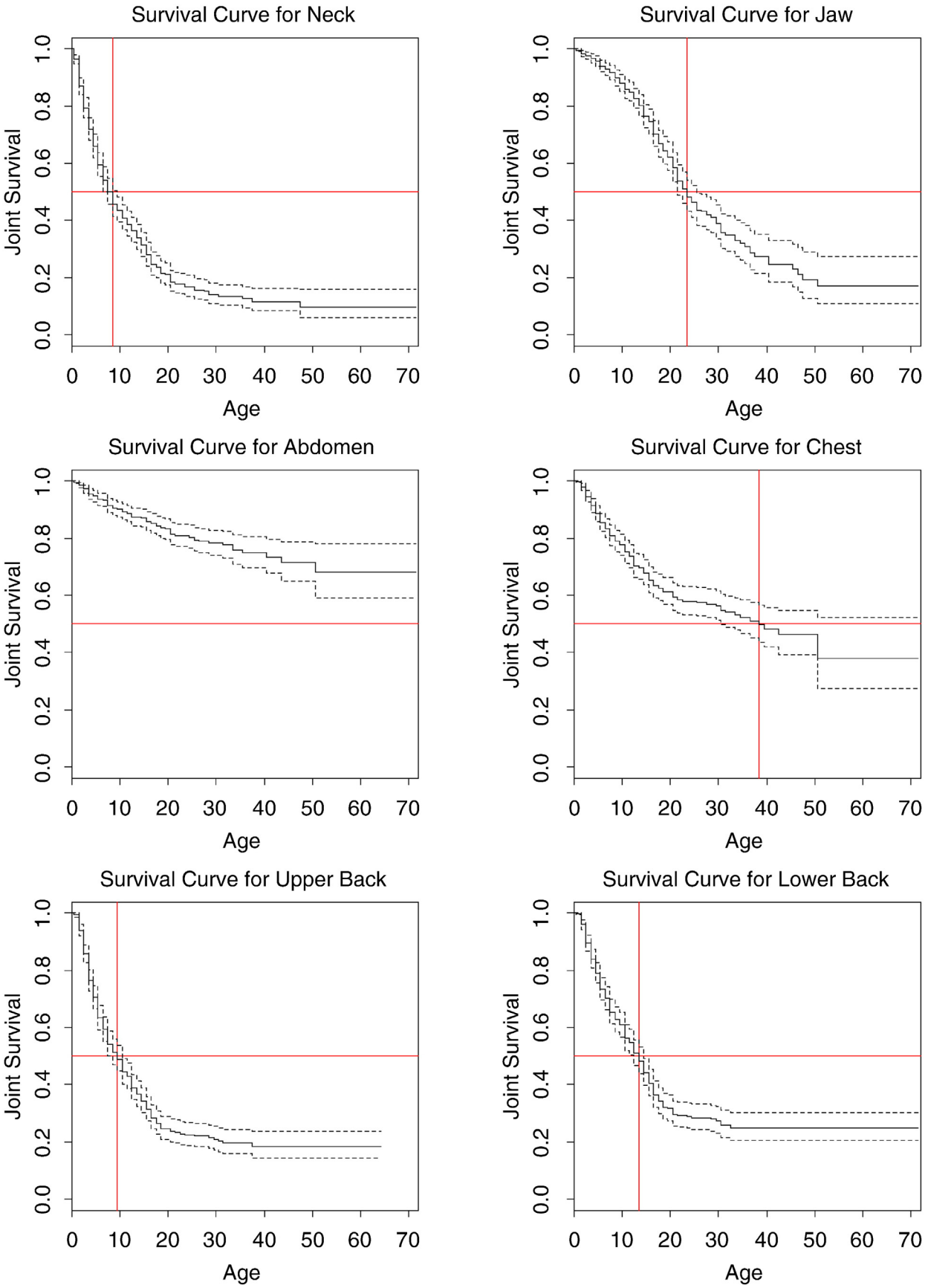

Fig. 2. Kaplan-Meier survival curve for the axial skeleton. The y-axis shows estimated survival (the proportion of respondents with that joint unaffected as of that age), the x-axis shows age in years. The solid black line is the estimated survival and the dashed lines show 95% confidence intervals. The red line indicates 50% survival, the age at which the estimated survival curve crosses the red line (if applicable) is the median age at which the joint is first affected. The median age at which each joint is affected is 8.5 years (neck), 23.5 years (jaw), 38.5 years (chest), 9.5 years (upper back) and 13.5 years (lower back). For the abdomen, the median is not reached because less than half of respondents have this area affected.

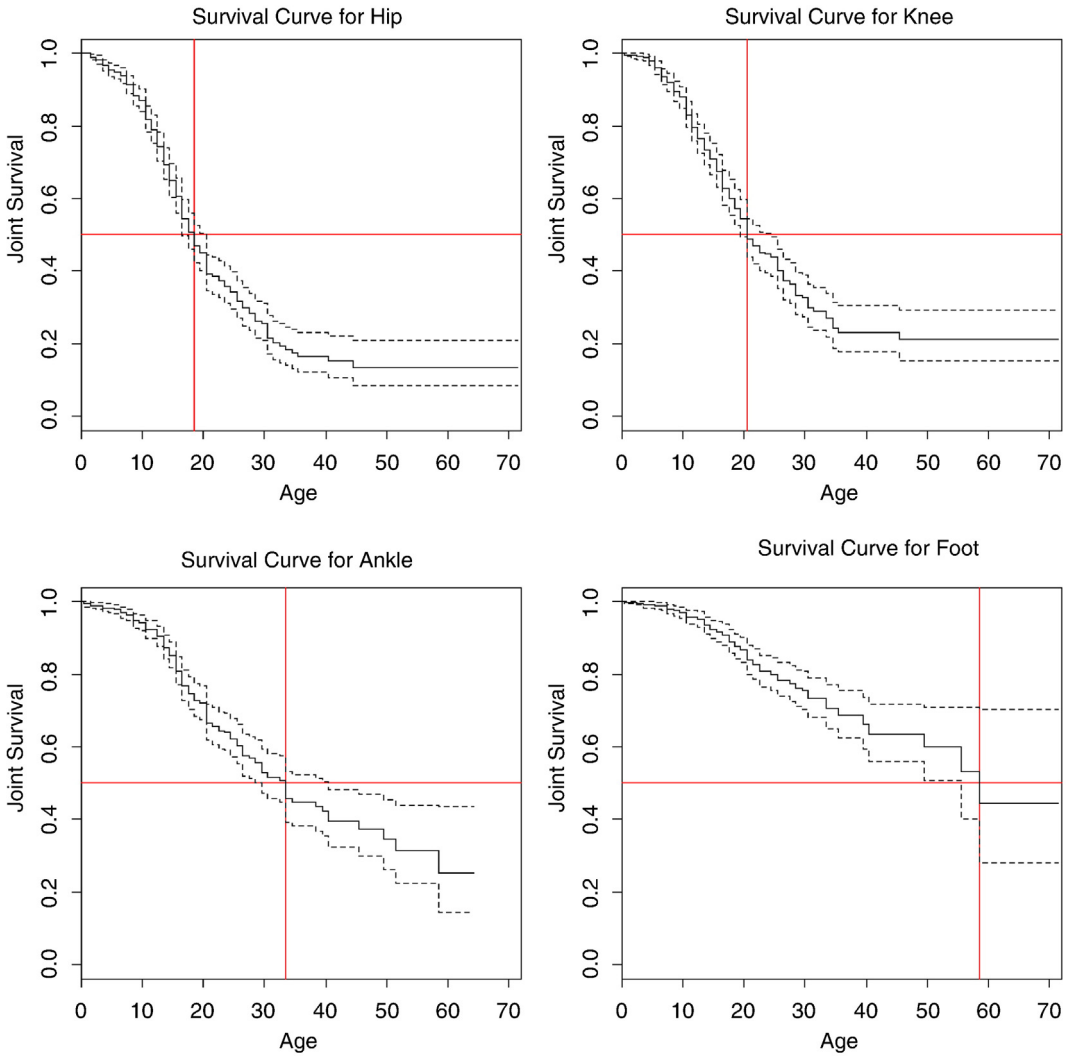

Fig. 3. Kaplan-Meier survival curves for the lower extremity. The y-axis shows estimated survival (the proportion of respondents with that joint unaffected as of that age), the x-axis shows age in years. The solid black line is the estimated survival and the dashed lines show 95% confidence intervals. The red line indicates 50% survival, the age at which the estimated survival curve crosses the red line (if applicable) is the median age at which the joint is first affected. The median age at which each joint is first affected is 18.5 years (hip), 20.5 years (knee), 33.5 (ankle) and 58.5 years (foot).

The hazard function for each joint was calculated as the probability of being affected at a given age, given that the joint has remained unaffected up to that age. Only ages 0 to 40 are plotted due to the paucity of information for ages over 40. For the abdomen, chest, neck, and upper back, the estimated hazard decreases over time. For the ankle, elbow, fingers, foot, hip, jaw, knee, lower back, shoulder, and wrist, the

Table 3
Annualized risk by joint and age.

Age (years)	1	5	10	15	20	25	30
Jaw	0.01 (0, 0.02)	0.02 (0.01, 0.03)	0.02 (0.01, 0.04)	0.03 (0.01, 0.04)	0.06 (0.03, 0.1)	0.06 (0.01, 0.1)	0.08 (0.01, 0.15)
Neck	0.10 (0.07, 0.12)	0.10 (0.07, 0.13)	0.06 (0.03, 0.1)	0.11 (0.06, 0.16)	0.12 (0.05, 0.19)	–	–
Upper Back	0.05 (0.03, 0.07)	0.10 (0.07, 0.14)	0.09 (0.05, 0.13)	0.08 (0.04, 0.13)	0.03 (0, 0.07)	–	–
Lower Back	0.04 (0.02, 0.05)	0.07 (0.05, 0.1)	0.08 (0.04, 0.11)	0.09 (0.04, 0.13)	0.07 (0.02, 0.11)	–	–
Chest	0.02 (0.01, 0.03)	0.04 (0.02, 0.05)	0.03 (0.01, 0.05)	0.04 (0.01, 0.06)	0.03 (0.01, 0.06)	–	–
Abdomen	0.01 (0, 0.02)	0.01 (0, 0.02)	0.01 (0, 0.02)	0.01 (0, 0.03)	0.02 (0, 0.04)	0.01 (0, 0.03)	–
Shoulder	0.03 (0.01, 0.05)	0.08 (0.05, 0.1)	0.12 (0.08, 0.16)	0.09 (0.05, 0.14)	0.09 (0.03, 0.15)	–	–
Elbow	0.01 (0, 0.02)	0.04 (0.02, 0.06)	0.05 (0.02, 0.07)	0.04 (0.01, 0.06)	0.08 (0.04, 0.13)	0.03 (0, 0.07)	–
Wrist	0 (0, 0)	0 (0, 0.01)	0.02 (0.01, 0.04)	0.03 (0.01, 0.05)	0.03 (0.01, 0.05)	–	–
Fingers	0 (0, 0)	0 (0, 0.01)	0.02 (0, 0.03)	0.01 (0, 0.02)	0.01 (0, 0.02)	0.02 (0, 0.03)	0.03 (0, 0.05)
Hip	0.01 (0, 0.02)	0.01 (0, 0.01)	0.06 (0.04, 0.08)	0.07 (0.03, 0.1)	0.13 (0.07, 0.18)	0.07 (0.02, 0.13)	0.15 (0.03, 0.25)
Knee	0 (0, 0.01)	0.02 (0.01, 0.03)	0.06 (0.03, 0.08)	0.05 (0.02, 0.07)	0.10 (0.05, 0.15)	0.08 (0.03, 0.13)	0.09 (0, 0.16)
Ankle	0 (0, 0.01)	0 (0, 0.01)	0.02 (0.01, 0.03)	0.05 (0.03, 0.08)	0.08 (0.04, 0.11)	0.03 (0, 0.06)	–
Foot	0 (0, 0)	0 (0, 0.01)	0.01 (0, 0.02)	0.01 (0, 0.01)	0.03 (0.01, 0.05)	0.02 (0, 0.04)	0.03 (0, 0.06)

The annualized risk of a joint being affected is defined as the conditional probability of an event in the next year, given that the joint has remained unaffected up to the indicated age. The table shows the annualized risk for each joint over time, estimated from the Kaplan-Meier survival curve, and 95% confidence intervals. Confidence intervals are estimated based on the formula for the variance of the log of the Kaplan-Meier estimate given in Greenwood [16]. The dashes are in age/joint combinations where there were not enough patients reaching that age without involvement of the particular joint.

Fig. 4. Hazard curves for the upper extremity. The y-axis shows the estimated hazard (the probability of a joint being affected at a given age, given that the joint has remained unaffected up until that age), the x-axis shows age in years. The solid black line is the estimated hazard and the dashed lines show 95% confidence intervals.

estimated hazard increases initially then either decreases or levels off. Hazard curves for each joint are shown for the upper extremity (Fig. 4), the axial skeleton (Fig. 5), and the lower extremity (Fig. 6).

3.4. Conditional joint involvement

Fig. 7A shows the conditional survival (conditional probability of having no further areas affected by age A + t, where A is the patient's current age and t is a time interval), given the patient's status at age A, for a hypothetical 12 year old subject with the neck, lower back, upper back, shoulder, and elbow already affected. For this patient, the estimated probability of all areas remaining unaffected for the next year is 0.79, and the estimated median time to the next area being affected is 3.5 years. Fig. 7B shows the conditional survival for another hypothetical patient, also age 12, with only the neck affected. For this patient, the estimated probability of all areas remaining unaffected for the next year is 0.58, and the estimated median time to the next area being affected is 1.5 years.

4. Discussion

We have produced joint survival curves for the upper extremity, axial skeleton and lower extremity using data from about 63% of the world's known population of FOP patients. This analysis reflects the age of the estimated fraction of individuals for whom a particular joint is not yet affected. Although there is no uniform pattern to joint dysfunction, there tends to be sequential involvement of axial regions (excepting the jaw) before appendicular regions, cranial regions before caudal regions, and proximal limbs before distal limbs. These general findings support earlier observations by Cohen et al. [19].

The most important difference in our analysis compared to that by Rocke et al. in 1994 [13] is the order of magnitude greater number of individuals surveyed and the consequent increased certainty of the observations. Compared to the 1994 data of 44 FOP patients [13], our current estimates of age- and joint-specific risks of new joint involvement are more accurate (narrower confidence limits) and are based on a wider range of ages. There is probably less bias in the current survey because it is much more comprehensive, capturing over three-fifths of the known FOP patients worldwide. Compared to the earlier survey, median ages for affected joints were older in the current sample, for all areas that were included in both surveys. The improved joint survival curves may reflect greater accuracy and less bias than those previously derived, but may also reflect the widespread use of steroids as a disease-modifying agent.

We have also summarized the data by the age at which about half of individuals have that joint affected (Table 2, Fig.8), although for some joints that is never reached (e.g., fingers). For example, by age 8.5, 50% of individuals with FOP are affected at the neck; by age 16.5, 75% of individuals are affected, with the last event at age 47. There were 5/35 individuals who had not been affected at the neck by age 47. By age 20.5, 50% of individuals with FOP are affected at the knees; by age 34.5, 75% affected, with the last event at age 45. There were 10/44 individuals who had not been affected at the knee by age 45. In contrast, not until age 54.5 are 50% of individuals with FOP are affected at the wrists, with less than 75% of individuals affected at the wrists and the last event at age 63. There were 2/4 individuals who had not been affected at the wrists by age 63.

For any given individual, precise predictions are not possible. For the neck, typically the earliest affected joint, 10% of individuals will be affected by one year of age, and an estimated 10% will not be affected until the late 40′s. The neck tends to be affected (median age 8) much earlier than the knees (median age 20), but still 77 individuals (15%) had the knees affected earlier than the neck. Thus, at any given time, one cannot predict how soon a joint will be affected, but rather which ones are most at risk.

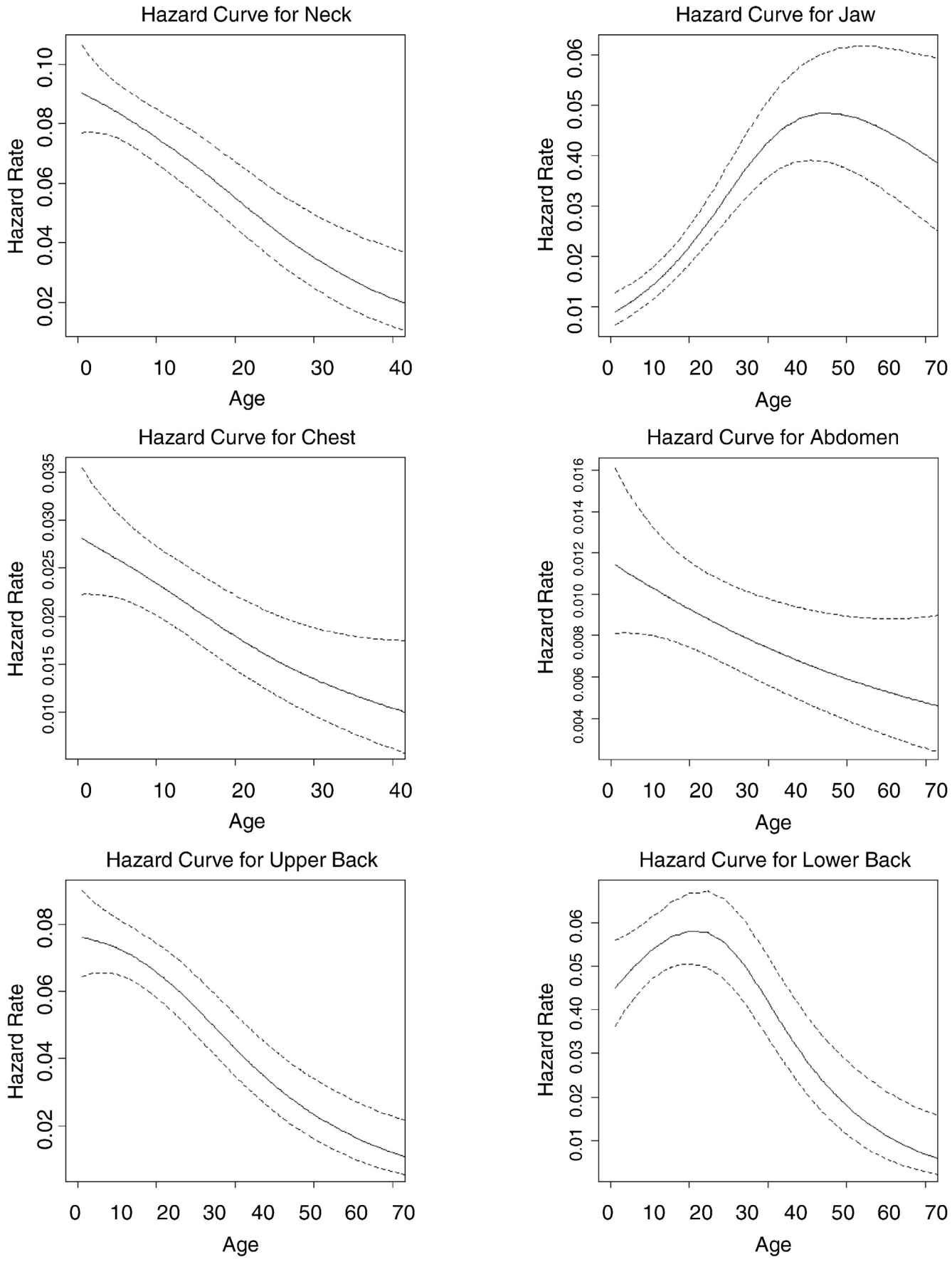

Fig. 5. Hazard curves for the axial skeleton. The y-axis shows the estimated hazard (the probability of a joint being affected at a given age, given that the joint has remained unaffected up until that age), the x-axis shows age in years. The solid black line is the estimated hazard and the dashed lines show 95% confidence intervals.

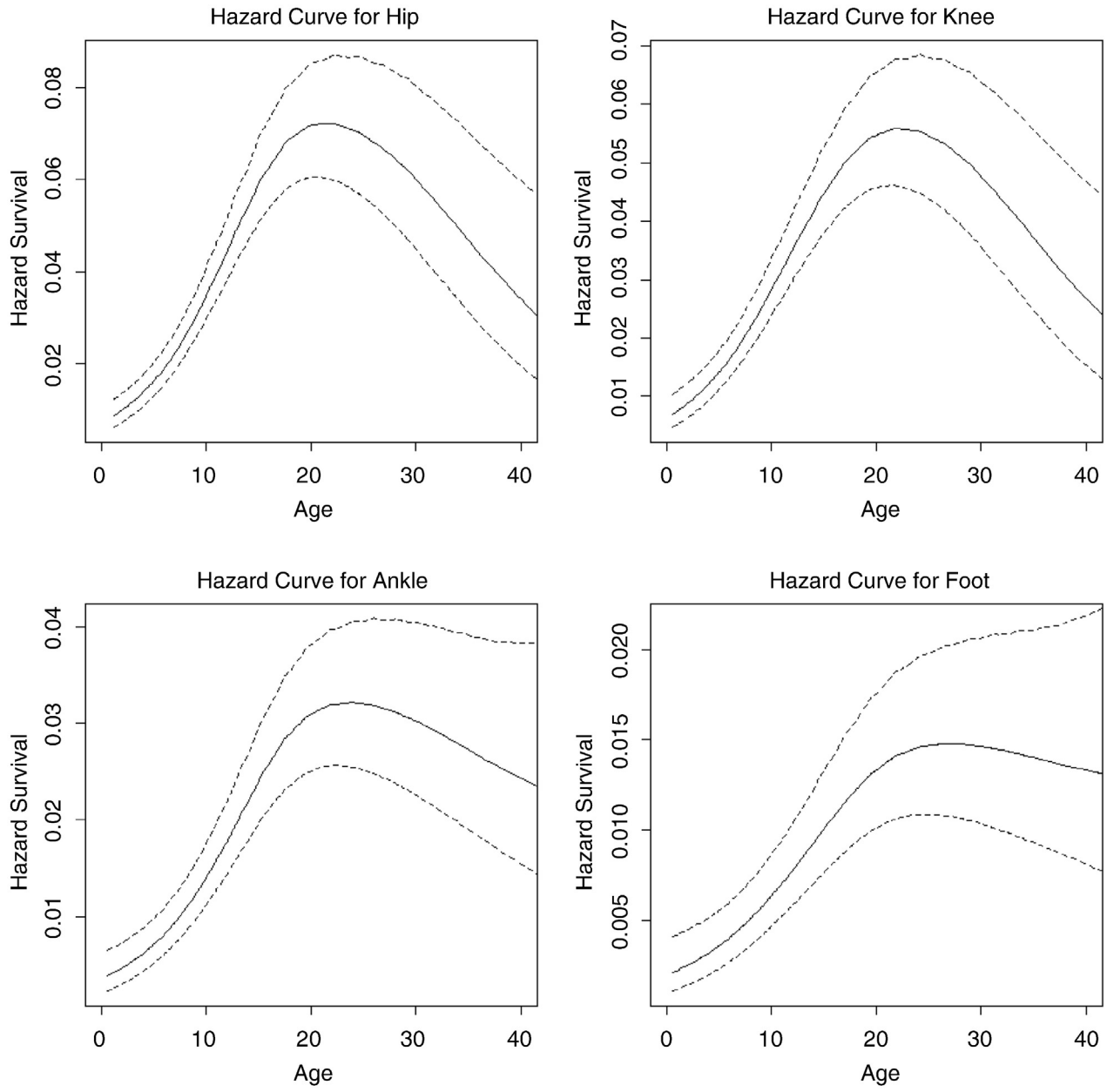

Fig. 6. Hazard curves for the lower extremity. The y-axis shows the estimated hazard (the probability of a joint being affected at a given age, given that the joint has remained unaffected up until that age), the x-axis shows age in years. The solid black line is the estimated hazard and the dashed lines show 95% confidence intervals.

Hazard curves can also be used to estimate the probability of a joint being affected at a specific age, and lend perspective on the likelihood of initial joint dysfunction over time. With the exception of the jaw and lower back, areas of the axial skeleton tend to display an estimated hazard that decreases over time, whereas the joints of the extremities tend to have an estimated hazard that increases initially then decreases over time.

Our natural history survey of 500 individuals with FOP, which encompasses approximately 63% of the world's known population of FOP patients [14], provided valuable new data for the assessment of joint dysfunction, including the set of improved joint survival curves presented here. These curves are the most accurate and unbiased to date. They will provide long-term forecasts and comparative statistics for future clinical study design.

5. Conclusions

We have determined estimates of risk for new involvement at any joint at any patient age, as well as the fraction of patients with uninvolved joints at any age based on data from over three-fifths of the world's known individuals with FOP. These estimates can be used to facilitate clinical trial design and to determine if potential treatments can modify predicted courses of joint dysfunction.

Conflict of interest

The authors declare that they have no competing interests.

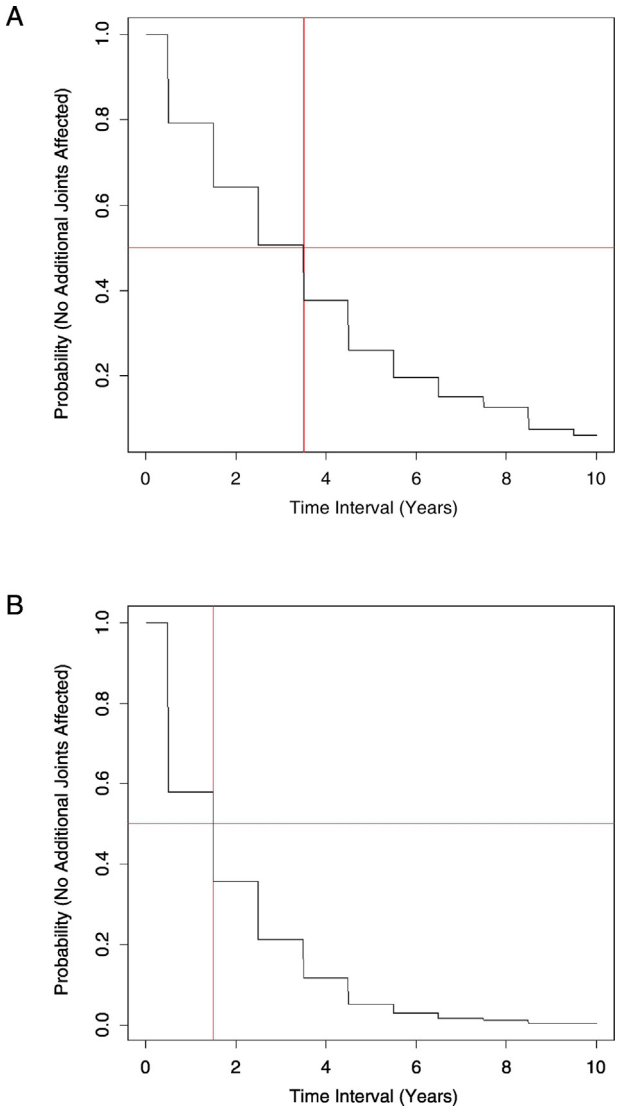

Fig. 7. Hypothetical examples of conditional joint survival. (A) The conditional survival (conditional probability of having no further areas affected by age A + t, where A is the patient's current age and t is a time interval), given the patient's status at age A, for a hypothetical 12 year old subject with the neck, lower back, upper back, shoulder, and elbow already affected. For this patient, the estimated probability of all areas remaining unaffected for the next year is 0.79, and the estimated median time to the next area being affected is 3.5 years. (B) The conditional survival for another hypothetical patient, also age 12, with only the neck affected. For this patient, the estimated probability of all areas remaining unaffected for the next year is 0.58, and the estimated median time to the next area being affected is 1.5 years.

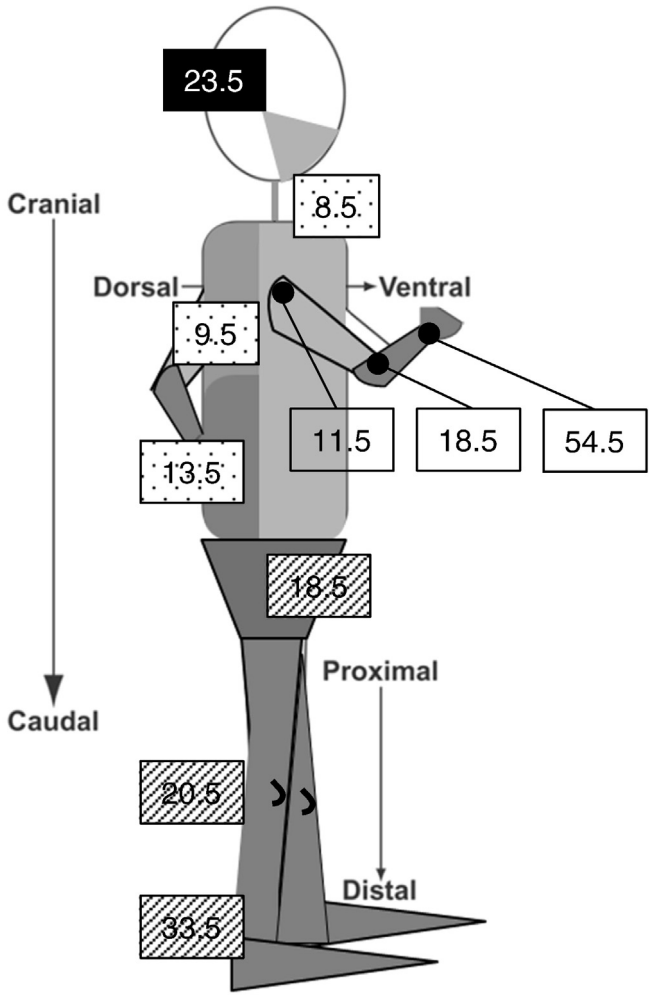

Fig. 8. Pictogram showing the median age at which each joint is affected in the upper extremity(white boxes), axial region (stippled boxes), and lower extremity (striped boxes). The median age at which the jaw is affected is depicted separately (black box) since it does not follow the same temporal pattern as other joints in the axial region.

Funding

This work was supported in part by the International Fibrodysplasia Ossificans Progressiva Association (IFOPA), the Center for Research in FOP and Related Disorders at the University of Pennsylvania Perelman School of Medicine, the Ian Cali Endowment for FOP Research, the Whitney Weldon Endowment for FOP Research, and the Isaac and Rose Nassau Professorship of Orthopaedic Molecular Medicine (to FSK); the Ian Cali Distinguished Clinician-Scientist at the Center for Research in FOP and Related Disorders at the University of Pennsylvania, the Robert and Arlene Kogod Professorship in Geriatric Medicine at the Mayo Clinic, and the Radiant Hope Foundation (to RJP); and the National Center for Advancing Translational Sciences, National Institutes of Health UL1 TR001860 and the University of California Davis School of Medicine (to DMR).

Authors' roles

Conception and design of the work were by FSK, RJP, and DMR. Collection and/or assembly of data were by FSK and RJP. Statistical analyses were performed by DMR and BPD-J. The manuscript was written by RJP, with revisions by all authors. Data interpretation was performed by all authors. The manuscript was approved by all authors.

Acknowledgements

The authors thank Mrs. Kamlesh Rai for her invaluable technical and administrative assistance.

References

[1] N. Bravenboer, D. Micha, J.T. Triffit, A.N. Bullock, R. Ravazollo, R. Bocciardi, M. di Rocco, J.C. Netelenbos, P. Ten Dijke, G. Sanchez-Duffhues, F.S. Kaplan, E.M. Shore, R.J. Pignolo, P. Seemann, F. Ventura, G. Beaujat, E.M. Eekhoff, G. Pals, Clinical utility gene card for: Fibrodysplasia ossificans progressiva, Eur. J. Hum. Genet. 23 (10) (2015).

[2] F.S. Kaplan, M. Le Merrer, D.L. Glaser, R.J. Pignolo, R.E. Goldsby, J.A. Kitterman, J. Groppe, E.M. Shore, Fibrodysplasia ossificans progressiva, Best Pract. Res. Clin. Rheumatol. 22 (1) (2008) 191–205.

[3] R.J. Pignolo, E.M. Shore, F.S. Kaplan, Fibrodysplasia ossificans progressiva: clinical and genetic aspects, Orphanet J. Rare Dis. 6 (2011) 80.

[4] R.J. Pignolo, E.M. Shore, F.S. Kaplan, Fibrodysplasia ossificans progressiva: diagnosis, management, and therapeutic horizons, Pediatr. Endocrinol. Rev. 10 (Suppl. 2) (2013) 437–448.
[5] E.M. Shore, M. Xu, G.J. Feldman, D.A. Fenstermacher, T.J. Cho, I.H. Choi, J.M. Connor, P. Delai, D.L. Glaser, M. LeMerrer, R. Morhart, J.G. Rogers, R. Smith, J.T. Triffitt, J.A. Urtizberea, M. Zasloff, M.A. Brown, F.S. Kaplan, A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva, Nat. Genet. 38 (5) (2006) 525–527.
[6] F.S. Kaplan, Q. Shen, V. Lounev, P. Seemann, J. Groppe, T. Katagiri, R.J. Pignolo, E.M. Shore, Skeletal metamorphosis in fibrodysplasia ossificans progressiva (FOP), J. Bone Miner. Metab. 26 (6) (2008) 521–530.
[7] F.S. Kaplan, M. Xu, P. Seemann, J.M. Connor, D.L. Glaser, L. Carroll, P. Delai, E. Fastnacht-Urban, S.J. Forman, G. Gillessen-Kaesbach, J. Hoover-Fong, B. Koster, R.M. Pauli, W. Reardon, S.A. Zaidi, M. Zasloff, R. Morhart, S. Mundlos, J. Groppe, E.M. Shore, Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1, Hum. Mutat. 30 (3) (2009) 379–390.
[8] M.R. Convente, H. Wang, R.J. Pignolo, F.S. Kaplan, E.M. Shore, The immunological contribution to heterotopic ossification disorders, Curr. Osteoporos. Rep. 13 (2) (2015) 116–124.
[9] F.S. Kaplan, R.J. Pignolo, E.M. Shore, Granting immunity to FOP and catching heterotopic ossification in the act, Semin. Cell Dev. Biol. 49 (2016) 30–36.
[10] H. Wang, C. Lindborg, V. Lounev, J.H. Kim, R. McCarrick-Walmsley, M. Xu, L. Mangiavini, J.C. Groppe, E.M. Shore, E. Schipani, F.S. Kaplan, R.J. Pignolo, Cellular hypoxia promotes heterotopic ossification by amplifying BMP signaling, J. Bone Miner. Res. 31 (9) (2016) 1652–1665.
[11] J.M. Connor, D.A. Evans, Fibrodysplasia ossificans progressiva. The clinical features and natural history of 34 patients, J. Bone Joint Surg. Br. 64 (1) (1982) 76–83.
[12] F.S. Kaplan, M.A. Zasloff, J.A. Kitterman, E.M. Shore, C.C. Hong, D.M. Rocke, Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva, J. Bone Joint Surg. Am. 92 (3) (2010) 686–691.
[13] D.M. Rocke, M. Zasloff, J. Peeper, R.B. Cohen, F.S. Kaplan, Age- and joint-specific risk of initial heterotopic ossification in patients who have fibrodysplasia ossificans progressiva, Clin. Orthop. Relat. Res. 301 (1994) 243–248.
[14] R.J. Pignolo, C. Bedford-Gay, M. Liljesthrom, B.P. Durbin-Johnson, E.M. Shore, D.M. Rocke, F.S. Kaplan, The natural history of flare-ups in Fibrodysplasia Ossificans Progressiva (FOP): A comprehensive global assessment, J. Bone Miner. Res. 31 (3) (2016) 650–656.
[15] E.L. Kaplan, P. Meier, Nonparametric estimation from incomplete observations, J. Am. Stat. Assoc. 53 (282) (1958) 457–481.
[16] M. Greenwood, The Natural Duration of Cancer Reports on Public Health and Medical Subjects, Her Majesty's Stationery Office, London, 1926 1–26.
[17] P. Rebora, A. Salim, M. Reilly, Bshazard: nonparametric smoothing of the hazard function. R package version 1.0, http://CRAN.R-project.org/package=bshazard 2014.
[18] R Core Team: A language and environment for statistical computing, http://www.R-project.org 2015.
[19] R.B. Cohen, G.V. Hahn, J.A. Tabas, J. Peeper, C.L. Levitz, A. Sando, N. Sando, M. Zasloff, F.S. Kaplan, The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. A study of forty-four patients, J. Bone Joint Surg. Am. 75 (2) (1993) 215–219.