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Causes of Death in Prader-Willi Syndrome: Prader-Willi Syndrome Association (USA) 40-Year Mortality Survey

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Abstract

Background—Prader-Willi syndrome (PWS) is a rare complex neurodevelopmental genetic disorder that is associated with hyperphagia and morbid obesity in humans leading to a shortened life expectancy. This report summarizes the primary causes of death and evaluates mortality trends in a large cohort of individuals with PWS.

Methods—PWSA (USA) mortality syndrome-specific database of death reports was collected through a cursory bereavement program for PWSA(USA) families using a brief survey created in 1999. Causes of death were descriptively characterized and statistically examined using Cox Proportional Hazards.

Results—A total of 486 deaths were reported (263 males, 217 females, 6 unknown) between 1973 and 2015 with mean age of 29.5 ± 16 years (2mo–67yrs), 70% occurring in adulthood. Respiratory failure was the most common cause accounting for 31% of all deaths. Males were at increased risk for presumed hyperphagia-related accidents/injuries compared to females and cardiopulmonary factors. PWS maternal disomy 15 genetic subtype showed an increased risk of death from cardiopulmonary factors compared to the deletion subtype.

Conclusions—These findings highlight the heightened vulnerability towards obesity and hyperphagia-related mortality in PWS. Future research is needed to address critical vulnerabilities such as gender and genetic subtype in the cause of death in PWS.

Keywords

Prader-Willi Syndrome; Mortality; Obesity; Cardiac and Respiratory Failure; Thromboembolism; GI-related Problems; Genetic Subtypes

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CONFLICTS OF INTEREST

The authors have no conflicts to declare.

INTRODUCTION

Prader-Willi syndrome (PWS) is a rare complex neurodevelopmental genetic disorder with multiple cognitive, behavioral and endocrine abnormalities and recognizable physical changes. PWS is characterized by a narrow bifrontal diameter, almond shaped eyes, short up-turned nose and down-turned corners of a dry mouth with sticky saliva, enamel hypoplasia and dental caries. Severe central hypotonia, a poor suck and feeding difficulties are cardinal features during infancy. Hypogonadism and hypogenitalism are noted in both males and females with cryptorchidism and a micropenis in males. Growth hormone deficiency leads to short stature and small hands with a flattened ulnar border and small feet. Hyperphagia or the unrelenting pathologic urge to consume food and unremitting hunger can lead to dangerous food-seeking behavior with life-threatening obesity, if uncontrolled.[1–5] Decreased muscle mass and increased fat mass are noted and accompanied by a low metabolic rate which is approximately 60% of normal.[1,2,6] There are limited treatment options available for the intractable obesity and hyperphagia which continues throughout adulthood and diminishes the quality of life for those with this disorder and family members. Delayed developmental milestones and mental deficiency (average IQ = 65) for the family background are noted with behavioral problems including tantrums, stubbornness, obsessive compulsions and skin picking frequently occurring in childhood and continuing into adolescence and adulthood.[1–3,7]

PWS is the most common known cause of morbid obesity in humans with prevalence between 1 in 10,000 to 30,000 live births.[1–3,7,8] The annual mortality rate is estimated at 1–4% with a shortened life expectancy greater than anticipated by their level of intellectual disability and due primarily to complications of hyperphagia and obesity-related causes.[8] The contribution of obesity as a cause of death in PWS is often discussed as a consequence of cardiorespiratory failure.[9] Food-related behavior increases the risk for mortality such as gastrointestinal perforation, aspiration/choking due to rapid consumption in combination with hypotonia-related swallowing difficulties, accidental deaths (e.g., traffic fatalities, hypothermia) and other physiological and genetic differences unique to this syndrome that further increase the mortality rate in PWS.[2]

PWS is caused by errors in genomic imprinting from lost expression of paternal genes in the chromosome 15q11-q13 region, most commonly due to a de novo deletion (about 70% of cases) followed by maternal disomy 15 (UPD15) or both 15s from the mother (about 25% of cases) with the remaining cases having imprinting defects.[2–5] Imprinting defects may be inherited with the potential of a 50% risk for subsequent children to have PWS. The PWS genetic subtypes include the most frequent paternally derived 15q11-q13 deletion consisting of the larger typical Type I or the smaller Type II deletion involving two different proximal 15q11-q13 breakpoints or rarely, atypically sized cytogenetic deletions.[2,5,10–12] Clinical and behavioral differences have been reported in those with the two typical Type I and Type II deletions and those with maternal disomy 15. Generally, those with PWS and the larger Type I deletion have more behavioral problems, obsessions and self-injury than those with the smaller Type II deletion or maternal disomy 15.[2,4,13–15] Reduced pain threshold further increases propensity toward self-injury and infection possibly related to disturbances in beta endorphin and substance P levels.[16] Differential behavioral and physiological profiles and

vulnerabilities may also be associated with maternal disomy 15 due to enhanced genetic activation with two maternally expressed alleles in the imprinted region or possible expression of recessive alleles.

Several clinical features in PWS suggest a role for hypothalamic dysfunction including eating disturbances (hyperphagia), growth hormone deficiency and small hands and feet with other endocrine problems, hypogenitalism and infertility.[1,2,17] These and other medical findings pose a risk for masking infectious diseases such as dysregulation of temperature[18] particularly in infants and young children with PWS and having septic shock within a short time span from presentation.[19,20] Infants with PWS who are hospitalized may also be at risk from complications related to medical care and treatment because of a narrow upper airway, possible aspiration, central hypotonia, hypoventilation, swallowing difficulties or gastroenteritis symptoms.

Herein, we report our experience in the largest study to date regarding the causes of death in PWS utilizing the PWSA (USA) syndrome-specific mortality survey database spanning the past 40 years.

METHODS

The Prader-Willi syndrome Association [PWSA (USA)] is a non-profit parent support organization founded by PWS families to supply information and assist or support families and others caring for those affected with this disorder. PWSA (USA) offers a bereavement program for PWS families in which supportive bereavement information is provided to families who contact the PWSA (USA) in the first and second years following a death. Data on causes of death have been collected through this cursory program using a brief survey created in 1999 and reported deaths have consistently been tracked through the bereavement coordinator since 2001. In 2005, a collaborative group of experts was created to develop a detailed questionnaire addressing research questions for families along with a release of medical records including relevant information regarding demographics, medical history, cause of death and autopsy reports and the circumstances around the time of death which were disseminated to families known to experience the death of a relative with PWS. The collected data were reviewed by the same examiners who are PWS experts. Inconsistencies in the data were reviewed and results clarified/confirmed by consultation with the reporting family member. The reported causes and contributors to each death and autopsy reports were evaluated by a clinically licensed cardiologist, parent and expert in the care of PWS who assessed the primary cause of death for each individual. The defined causes of death were then classified in major categories.

Statistical Analysis

Causes of death in PWS fell into 13 categories which were descriptively characterized (e.g., frequencies, means with standard deviations) by gender, age and body mass index (BMI) at death and PWS genetic subtype. The frequency of the 13 individual causes of death were summarized and reported for four age groups: infants (newborn to <3 yrs); children (3 to <12 yrs); adolescents (12 to <18 yrs) and adults (18 yrs and over). Causes of death were further subclassified after reviewing the dataset as Cardiopulmonary in origin which

included all deaths due to cardiovascular, respiratory causes and pulmonary embolisms; or presumed causes considered Hyperphagic in origin which included gastrointestinal problems, choking and accidents likely to have resulted from food seeking behaviors (e.g., crossing a street carelessly to gain access to a restaurant). Mortality trends in the age of death were also considered over time based upon the year the death occurred in order to assess cohort effects related to changes in diagnostic capabilities and treatment.

Descriptive characterization including frequencies, means with standard deviations and all statistical comparisons were performed using SAS Statistical Software version 9.4 (Cary, NC). Pearson correlation and analysis of variance (ANOVA) were utilized for continuous variables while bivariate and multivariate analyses of dichotomous, ordinal data utilized chi squared and logistic regression modeling. Cox Proportional Hazards ratios and log rank testing were applied to model mortality risk as a function of the age at death and for the generation of Kaplan-Meier curves to test the effects of gender (male vs female), cause of death (cardiopulmonary vs hyperphagia) and PWS genetic subtype (deletion or maternal disomy 15) on mortality risk.

RESULTS

Our investigations compiled family-reported deaths occurring between 1973 and 2015 for 486 individuals with PWS [N=263 (54%) Male; N=217 (45%) Female; N=6 (1%) unknown; Table 1]. The age of mortality was noted for 425 subjects with an average of 29.5 ± 16 years and ranged between 2 months and 67 years and significantly lower among males (28 ±16 years) compared with females (32 ±15 years) ($F=6.5$, $p<0.01$). The majority of reported deaths occurred in adulthood (N= 338, 70%) with only 20% of deaths observed among individuals under the age of 18 years. This relationship was true even after consideration of cohort effects and changes in reporting/diagnostic capabilities with time. The distribution of adult deaths was evenly divided (50/50) between males and females while male gender predominated significantly among the younger age groups (64/36 male to female; $\chi^2=5.7$, $p<0.02$).

The year of death was available for 440 (90%) respondents (N=203 females; N=234 males; N=3 unknown); mean age of death was reported for 425 (87%) respondents (N=199 females; N=224 males; N=2 unknown) and a more precise cause of death was provided for 312 (64%) individuals (N=137 females; N=174 males; N=1 unknown) reported with PWS. PWS genetic subtype data were available for 10% of individuals and composed primarily of the deletion subtype. The mean age of mortality was positively correlated with the year of death ($r=0.12$, $p<0.01$) in the overall sample suggesting increased lifespan possibly related to improvement in medical care with time and earlier diagnosis, but this relationship was driven by an effect in females (year of death, $r=0.20$, $p<0.005$). There was no significance noted when males alone were considered (year of death, $r=0.05$, $p=0.49$, see Figure 1).

Causes of Death

A precise cause of death was available for 312 of the 486 cases and divided into 13 categories (see Figure 2). Those with and without a known cause of death did not significantly differ by gender or age of death. Considering only those with a known cause of

death, the most common single cause of death was due to respiratory failure and reported in N=98 individuals (31%) followed by cardiac disease/failure (N=51, 16%), gastrointestinal (GI) related problems such as perforation, distension or obstruction (N=31, 10%) and infections (N=29, 9%). Obesity was listed as a cause of death for 22 cases (7%) and pulmonary embolism was reported for 21 cases (7%). Additional categories reflected disease-associated behavioral risks from choking, accidents and hypothermia possibly related to food seeking and consumption. There were no significant differences in the frequency of male vs female gender for any individual cause of death.

Causes of death in PWS varied according to age range with reported respiratory failure as the leading cause of death for all groups and presumed obesity-related, cardiopulmonary factors contributed to more than half of all deaths (see Supplement 1). Deaths due to obesity-related factors such as cardiovascular disease and failure, pulmonary embolism and renal failure appeared in childhood and increased in adolescence through adulthood while deaths due to GI problems and infections were stable at approximately 10% through the life span. Additional morbidity possibly related to food seeking (e.g., accidents, choking) appeared in childhood and adolescence contributing to approximately one third of all deaths and approximately half of the (predominantly male) deaths under the age of 18 years. The BMI at the time of death was identified for 132 cases with an average of 49±23 kg/m^2 and range of 14–122. Standardized mean BMIs were well above normal (>90th percentile).

PWS Genetic Subtype

Investigation of the relationship between PWS genetic subtype and cause of death was hindered by lack of necessary genetic characterization among the selected sample particularly in the older individuals who may not have had access to accurate genetic testing. DNA methylation testing which is 99% accurate in confirming the diagnosis of PWS but will not determine the specific genetic subtype (chromosome 15q11-q13 deletion, maternal disomy 15 or imprinting defects) did not become readily available until the mid to late 1990s.[21,22] The deletion subtype was approximately equally divided among male (N=14, 45%) and female (N=17, 55%) cases with a mean of 34.8±16 years of age at death which was not related to the year in which the death occurred. However, the age of death for individuals with the deletion subtype was significantly higher among females (41.0±13.3 years, range 14.7–55.3 years) than males (27.2±16 years, range 0.97–59 years; $t=2.0$, $p<0.05$). The leading causes of death associated with the deletion subtype were cardiac problems (N=9, 30%), respiratory failure (N=8, 27%) and infections (N=5, 17%) followed by GI-related problems (N=4, 13%), pulmonary embolism (N=2, 7%), choking (N=1, 3%) and hypothermia (N=1, 3%) with females comprising 7 of the 9 cases of cardiac problems and 5 of 8 cases of respiratory failure in the deletion subsample. The limited data from uniparental maternal disomy 15 showed 8 of the 12 cases (9 male; 3 female) died from respiratory failure while the remaining 4 cases (3 male; 1 female) died from GI-related problems, cancer, infections and renal complications, respectively at a mean of 22.2 ± 18 years ranging from 1.2 to 49 years which did not differ by gender. A single male with an imprinting defect died from GI perforation at 13 years of age.

Survival Analyses

Cox regression analysis of our sample of 425 individuals with PWS and a known age at death identified quartile point estimates for 25% mortality of 20 years of age [95%CI (18–21yrs)]; 50% mortality of 29 years of age [95%CI (27–32yrs)]; 75% mortality of 42 years of age [95%CI (39–44yrs)]. A 99% percent mortality rate was achieved by 60 years of age. A primary sex difference in mortality risk was identified in PWS with males displaying a significantly increased risk of early mortality compared to females [χ^2=5.0, p<0.025; hazard ratio=1.2 (95%CI 1.0, 1.5); Figure 3A]. Further, sex significantly interacted with the primary cause of death (cardiopulmonary vs hyperphagic) with males showing significantly increased risk of death due to presumed hyperphagia-related causes (accidents, choking, GI-problems) relative to females (Figure 3B; Supplement 2). There was a near-significant trend towards increased risk for cardiopulmonary vs hyperphagia-related deaths among females. PWS genetic subtype also significantly impacted mortality risk over the lifespan with individuals possessing the maternal disomy 15 subtype showing a significantly increased risk [HR=2.0 (95%CI 1.0 to 3.9); χ^2 =4.1, p<0.04] of death due to cardiopulmonary vs hyperphagic causes compared to the deletion subtype (Figure 4).

DISCUSSION

We report a descriptive analysis of mortality data collected from individuals with Prader-Willi syndrome with reported deaths between 1973 and the year 2015 as part of a supportive bereavement program for PWS families. Respiratory failure was the most common overall cause of death reported in our database of adults and children with PWS while cardiac disease and failure with pulmonary thromboembolisms were more commonly found in adulthood in combination with obesity-related morbidity. Further, this is the first report to characterize and quantify deaths attributable to pulmonary embolism in Prader-Willi syndrome which accounted for 7% of all deaths. Cardiopulmonary and BMI-related mortality factors predominated among females while males were more likely to experience accidents, choking and infection at a young age. Accidents, aspiration, sepsis and choking were the most common causes of death seen in PWS children and adolescents accounting for about half of deaths in childhood and one third of adult deaths. A progressive increase in life span (measured as age of mortality) was observed over time particularly for deaths due to cardiac problems in females possibly due to protective effects associated with earlier diagnosis, treatment intervention and monitoring (e.g., growth hormone) and weight management of recent cohorts. This was not observed among males possibly due to an increased rate of hyperphagia-related rather than obesity-driven cardiopulmonary deaths among males with PWS. A significantly increased risk of mortality due to cardiopulmonary factors was observed for maternal disomy 15 compared to deletion genetic subtypes which may reflect differential vulnerability due to amplified effects of homozygous mutations from duplicated maternal contributions on chromosome 15.

Despite the report of causes of death in PWS in individual case reports, case series, population surveys and syndrome-specific registry databases in both children and adults, there is a paucity of data of systematic collection and analysis of causation of death. For example, the Cambridge PWS study reported in 2004 on fewer than 100 individuals with

confirmed PWS found a mortality rate of 3% per year after the age of 5 years. More recently, Lionti et al.[23] in 2012 reviewed an Australian registry of 163 individuals with PWS from 3 weeks to 60 years and 15 deaths were recorded which corresponded to an 87% probability of survival to 35 years of age which equates to a survival rate reported from an Italian survey of 80% at 40 years of age for 425 individuals with PWS. The most common causes of death were the following in no particular order: pulmonary thromboembolism; sepsis; accidents; diabetes; cardiac disease and problems; choking; aspiration; gastric rupture; respiratory failure and obesity-related complications.[23–30]

The present summary of mortality in PWS is consistent with earlier reports indicating the young age of death and high rates of mortality due to cardiac and respiratory failure. Deaths attributable to obesity-related and cardiac disease can be anticipated for this highly vulnerable group and our data suggest early interventions have impacted disease trajectory resulting in delayed mortality (i.e., older age of death) among females. However, the underlying pathology for respiratory failure – the leading cause of death for adults and children remains elusive and does not appear to be impacted by recent advancements in treatment modalities. Reported deaths due to respiratory failure also could be secondary to undiagnosed aspiration, pulmonary embolism or some unspecified neurological disturbance and may vary by gender and/or age. Future targeted research should seek to characterize this phenomenon to advance treatment development. Similarly, individuals with PWS show high rates of choking, accidents and GI-perforation presumably related to uncontrolled hyperphagia and food seeking behaviors contributing to about one third of all reported deaths and about one half of the deaths in childhood. Accidental and/or hyperphagia-related deaths appear to disproportionately impact younger males possibly due to increased activity and/or impulsive characteristics.

Early diagnosis of PWS and prevention of overweight are key factors in preventing early causes of death in individuals. These include close monitoring and supervision of food access and quantity to avoid choking which can occur from eating quickly and gastric rupture resulting from excessive food consumption The risks associated with choking are increased in the PWS population compared with normal[27] with potential causes of increased choking related to poor oral/motor coordination, poor sensation, hypotonia, hyperphagia, a dry mouth, decreased mastication and voracious feeding habits. Therefore, implementation of preventive measures, and education with better awareness of group home care providers are recommended for all individuals with PWS including training for use of the Heimlich maneuver, supervised meals, food security along with food preparation and diet modification. Operational strategies should incorporate sips of fluids between bites within meals to help clear the esophagus to lessen the risk choking episodes. Pain in the upper abdomen and/or vomiting should be taken as a possible sign of an emergent event such as acute serious gastric/intestinal dilatation with risk for rupture in PWS. An established algorithm for evaluating individuals with PWS and GI complaints available at www.pwsausa.org should be followed along with intravenous support.

In adults, weight reduction is complicated by daytime sleepiness as a result of apnea. Adults with PWS and obesity can be expected to have the same life-threatening complications as those obese individuals without PWS including complications from cardiopulmonary

problems, hypertension, diabetes and skin infections.[31] The reduction of weight reduces the risk of obesity-related and possibly life-threatening complications.

As hyperphagia and subsequent obesity are cardinal features of this rare genetic disorder, excessive overeating, stomach necrosis and rupture, cardiovascular disease, respiratory failure, sleep apnea and diabetes mellitus and related co-morbidities can be life-threatening. Early diagnosis, dietary intervention with restricted caloric intake and significant controls on access to food (locking cabinets, etc) with established exercise programs for each person with PWS have led to successful weight loss and BMI reduction; active management of hyperphagia prolongs life. Furthermore, the use of growth hormone and other hormone replacements have helped to normalize body composition and stature in PWS with a positive impact on the control of obesity.

In summary, causes of death seen in infancy or young childhood in PWS are more likely to be related to respiratory failure, aspiration, infection and choking than obesity-related factors while cardiac disease and failure, pulmonary thromboembolism, accidents, sepsis and obesity-related complications are more commonly found in adolescents and adulthood. Deaths from cardiac disease typically reflect right heart failure rather than atherosclerotic disease. Males may be more likely to engage in aggressive or risky food seeking behaviors than females particularly in childhood while females may be more likely to suffer obesity-related morbidity. Syndrome-specific standardized growth charts developed for growth hormone treated individuals with PWS appear to show differences in the degree of obesity (weight) between males and females. At 18 years of age, females were heavier than PWS males at the same age.[32]

Our analyses and interpretation of data trends are limited by the reliability of death reporting based upon the availability and knowledge of family members and access to confirmed genetic status and autopsy reports. Older individuals without living relatives to report the death may have been underreported. Similarly, deaths in infants and children with PWS, prior to better awareness with recognition of PWS and the availability of advanced genetic testing, may have escaped diagnosis prior to death. Statistical corrections for age and time effects have been incorporated to minimize the influences of these factors on our conclusions but the sample size is small. Gender differences in PWS genetic subtype may have influenced the result. Never-the-less, this study represents the largest and most extensive examination of mortality in PWS to date and the results support current understanding of disease pathology and mortality in PWS and provide useful insight into risk factors, mortality trajectory over time and areas of need. Family members, care providers and health care professionals involved with the immediate and long term care of individuals with PWS should be made aware of these risk factors and causation of death to improve the longevity and quality of life for those with PWS (at all ages) and family members.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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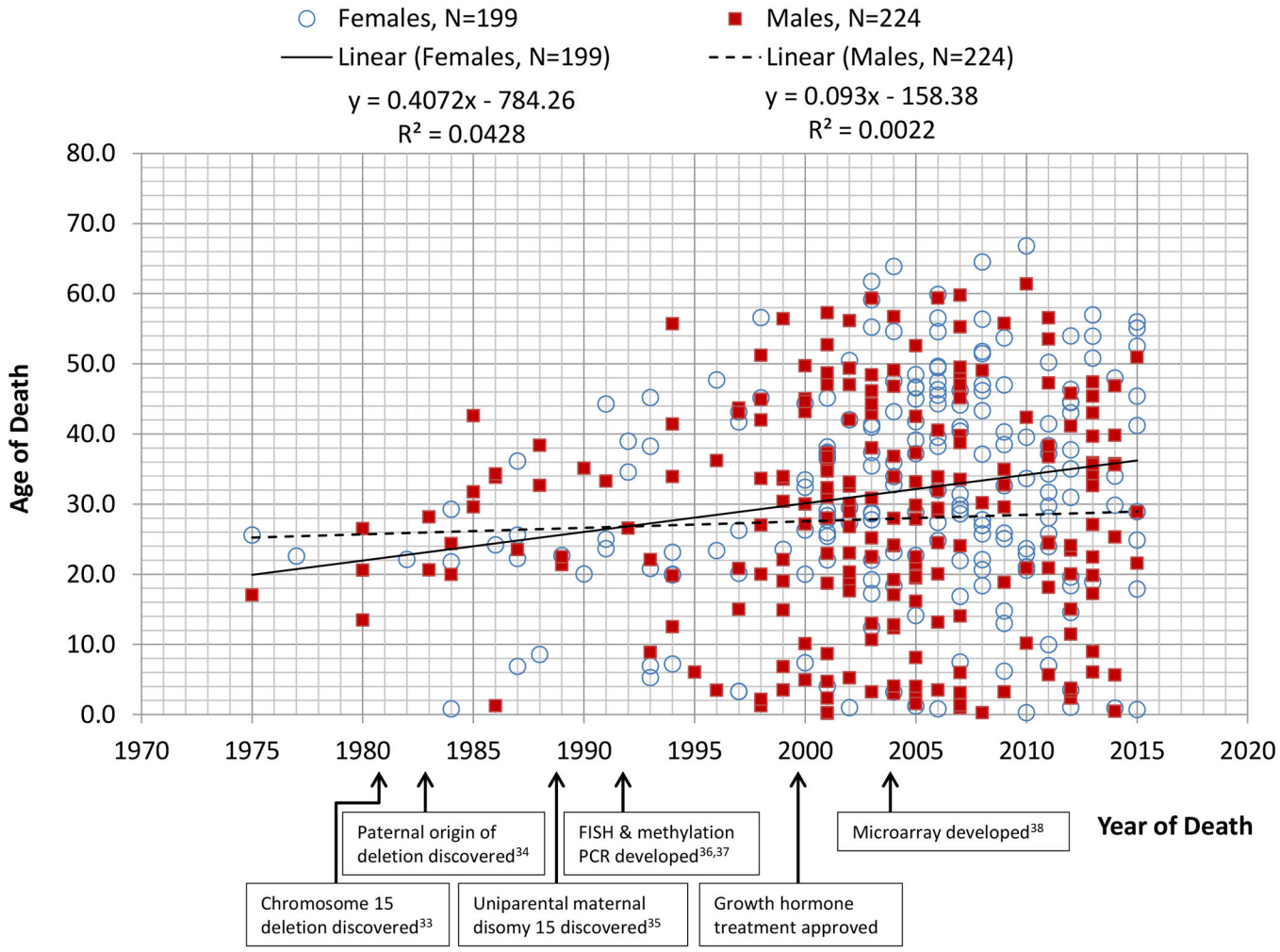

Figure 1.

Relationship between the reported age and year of death in Prader-Willi syndrome. Scatter plot of the age at death by the year of death for males (red squares) and females (circles) with Prader-Willi syndrome (PWS) with respect to historical benchmarks in genomic discovery and treatment advances in PWS. Trend lines show the correlation coefficient for females (solid line) and males (dotted line).

Category	Mean Age (SD)
Respiratory Failure, N=94	24.6 (16) yrs
Cardiac, N=50	32.1 (14) yrs
GI, N=30	32.4 (16) yrs
Infection, N=29	35.7 (16) yrs
Obesity, N=22	30.7 (12) yrs
Pulmonary Embolism, N=19	34.1 (12) yrs
Choking, N=18	30.1 (17) yrs
Accident, N=17	25.0 (16) yrs
Renal Failure, N=7	34.2 (11) yrs
Neurologic, N=6	18.0 (21) yrs
Hypothermia, N=3	30.8 (14) yrs
Drug Reaction, N=3	25.1 (9) yrs
Cancer, N=4	39.7 (27) yrs

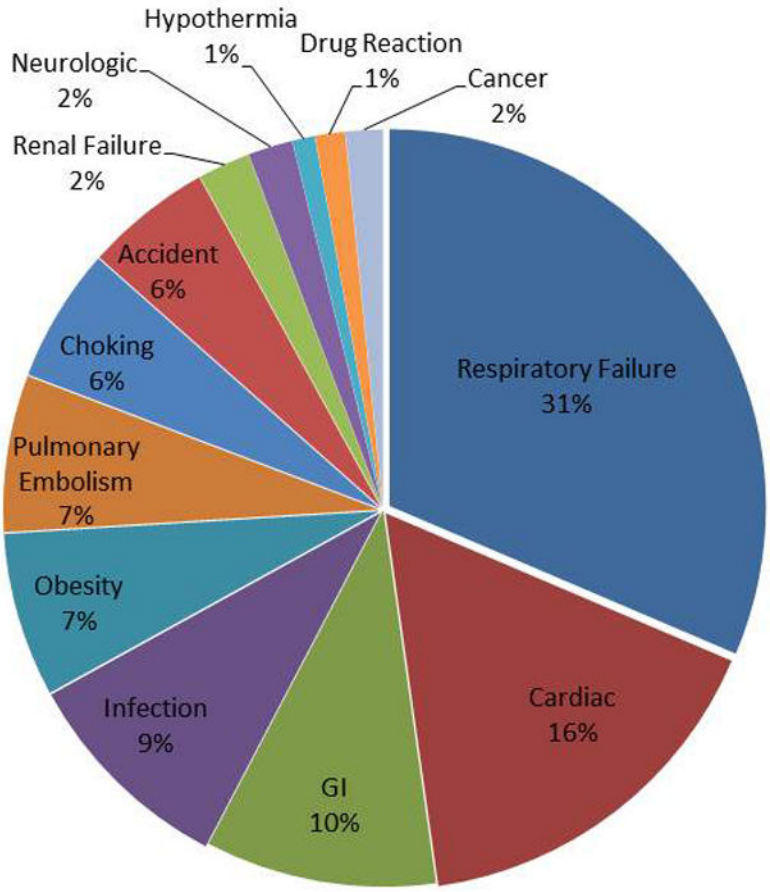

Figure 2.
Causes of death among 312 individuals with Prader-Willi syndrome divided into 13 major categories.

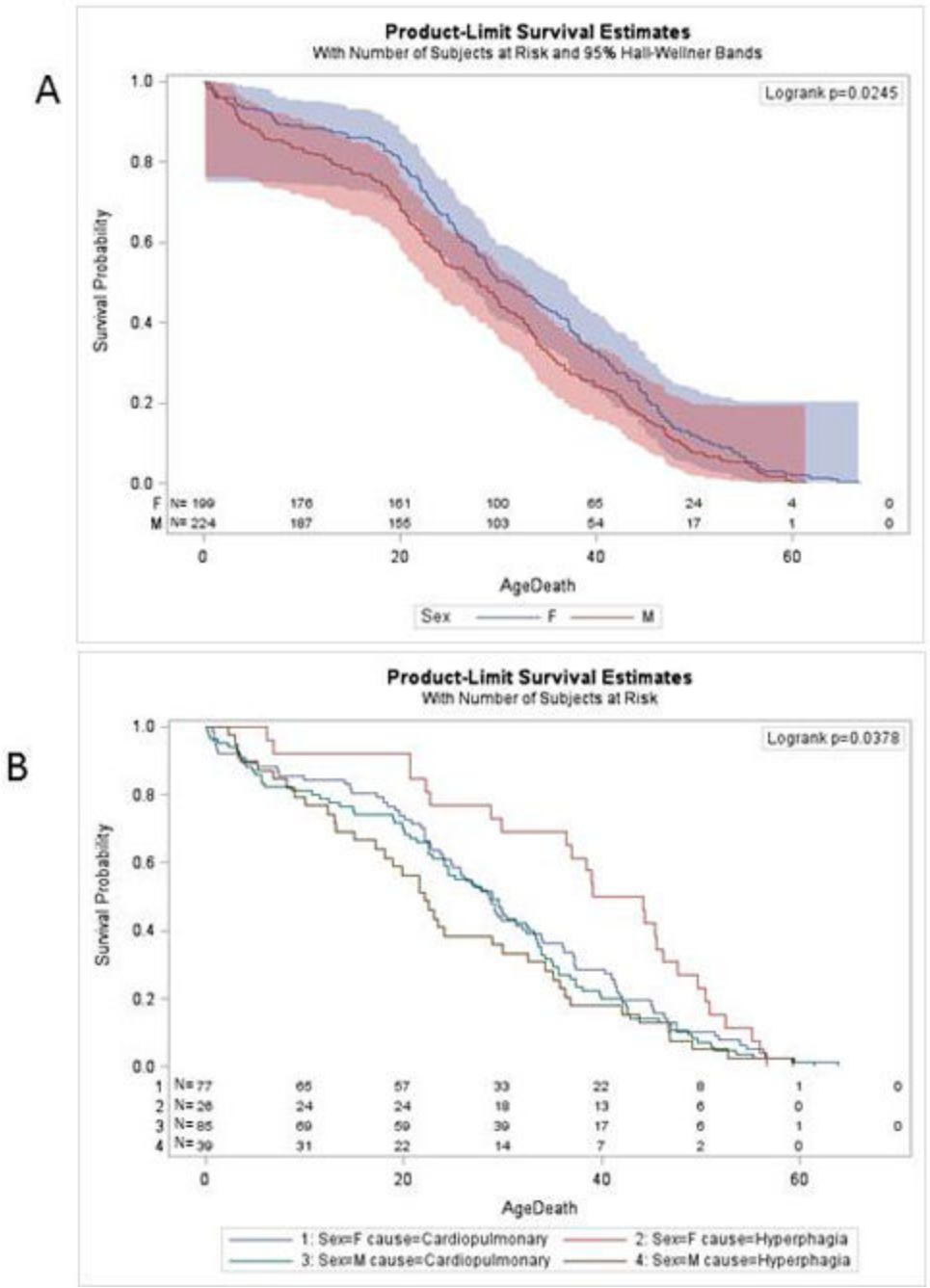

Figure 3.

Survival analysis illustrates the effects of gender and cause of death on age of death in Prader-Willi syndrome. Kaplan-Meir plot of survival probability is shown as a function of age at death for **A**) males vs females with 95% Hall-Wellner Bands and for **B**) cardiopulmonary vs hyperphagia-related causes by gender. The number of uncensored participants by group are listed at the bottom of each figure.

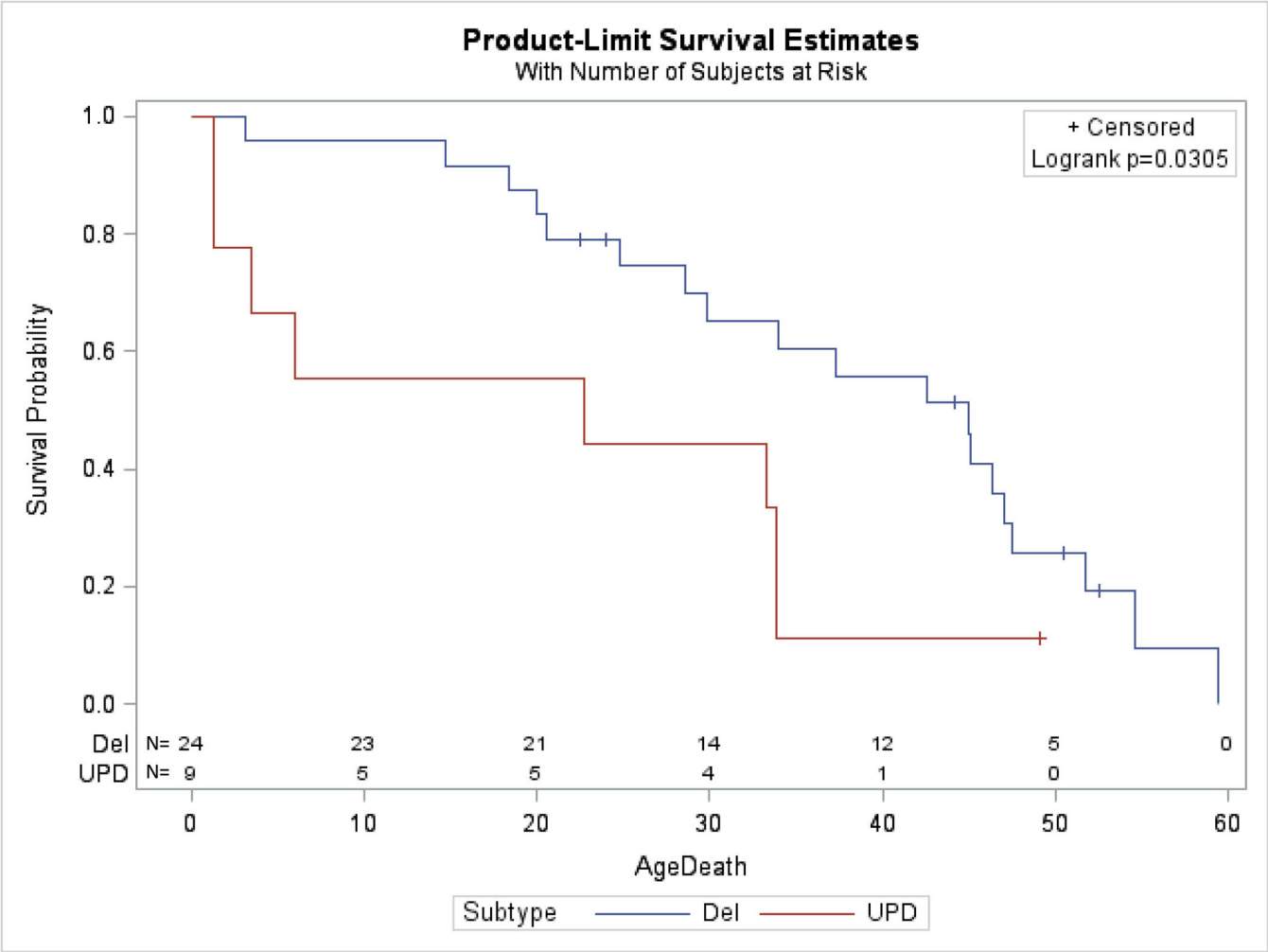

Figure 4.

Survival analysis of deaths due to cardiopulmonary causes as a function of Prader-Willi syndrome (PWS) genetic subtype. Kaplan-Meir plot of survival probability is shown for deaths attributable to cardiopulmonary vs hyperphagia-related causes for individuals with 15q11-q13 deletion (Del) vs maternal uniparental disomy 15 (UPD). The number of uncensored participants by PWS genetic subtype are listed at the bottom of the figure.

Table 1

PWSA(USA) 40-Year Mortality Survey Syndrome-Specific Database Summary

Characteristic, Total N=486	**Value**
Gender, N=480 (99%)	N=263 (54%) Male N=217 (45%) Female
Age of death, N=425 (87%) Male, N=224 (53%) Female, N=199 (47%)	Mean (±SD)= 29.5 (±15) years (range 2 mo − 67 yr) Mean (±SD)= 27.8 (±16) years (range 1 mo − 61 yr) Mean (±SD)= 31.7 (±15) years (range 2 mo − 67 yr) {F=6.5 P<0.011(gender)}
Age range	Infant (<3yrs), N=21 (4%); N= 13 (62%) Male Child (3–12yrs), N=43 (9%), N=28 (65%) Male Adolescent (12–18), N=23 (5%), N=15 (65%) Male Adult (18+ yrs), N=338 (70%), N=168 (50%) Male Undefined, N=61 (12%)
Year of death	N=440 (90%); See Figure 1
Cause of death	Known cause, N=312 (64%), 13 categories (see Figure 2) Unknown cause, N= 174 (36%)
PWS subtype, N=48 (10%)	Deletion, N=31 Uniparental maternal disomy 15, N= 14 Imprinting defect, N=1 Acquired through injury/surgery, N=2 Unknown genetic subtype, N=438
Autopsy performed	N=40 (8%)
Body mass index (kg/m^2), N=132	Mean (±SD)= 49.3±23 (range 14 − 122) kg/m^2 Mean (±SD)= 92±16 (range 3 − 99) percentile