Epidemiologia dell'Iperparatiroidismo

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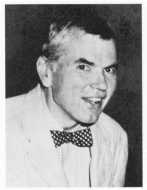
Conflicts of interests

No disclosures

Primary Hyperparathyroidism: changing over time

Back in the dark ages of endocrinology, in the early 1920's, hyperparathyroidism was an unknown fact. We can think of it as an open circle waiting to be filled in.



Fuller Albright

The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME 8 AUGUST, 1948 NUMBER 8

A PAGE OUT OF THE HISTORY OF HYPERPARATHYROIDISM*

FULLER ALBRIGHT, M.D.
Massachusetts General Hospital, Boston, Massachusetts

MEMBERS of the Association for the Study of Internal Secretions and Guests!

Two years ago, when I became president-elect of this association, I knew I would have to give this address this evening. I have worried about it ever since and am still worrying. The occasion seemed to call for something a little different than the presentation of new data. A heavy philosophical treatise, were I capable of producing such, also seemed inappropriate. I finally decided on a short historical note which is of interest not only for the facts discovered but for the means by which they were arrived at.

PATHOLOGICAL VERSUS PHYSIOLOGICAL APPROACH

What I am about to say should not be taken too literally by any pathologist or physiologist who happens to be present.

In a sense, the pathologist and physiologist approach an endocrinological problem from opposite sides. The former starts with the completed picture of the disease, learns to associate such-and-such changes in some endocrine gland with the disease, and finally comes out with a cause-and-effect relationship between the gland and the disease process in question; the latter determines what such-and-such a hormone does and deducts therefrom what the result of an under- or over-function of said hormone would be.

Received for publication June 7, 1948.

* Presidential Address delivered at the Twenty-ninth Annual Meeting of the Association for the Study of Internal Secretions on June 6, 1947, in Atlantic City, New Jersey.

CLINICAL TYPES OF DISEASE

Depending on whether the urinary tract or skeletal involvement predominates and the degree of change present in each system, it is possible to describe several different types of the disease.

Classic Hyperparathyroidism (von Recklinghausen's disease).—Skeletal symptoms predominate and consist of decalcification, cysts, tumors and, eventually, fractures (five cases in this series).

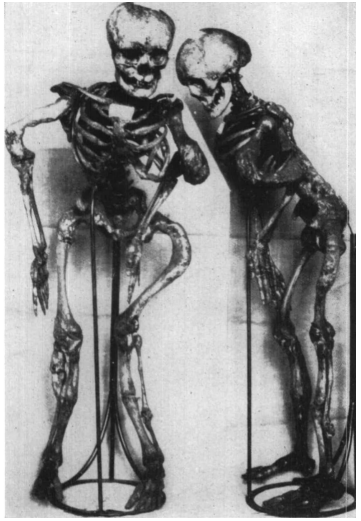
Osteoporotic Form of Hyperparathyroidism.—Presenting symptoms are due to generalized decalcification and there are no cysts or tumors (two cases in this series).

Hyperparathyroidism with Nephrolithiasis.—Presenting symptoms are associated with renal stones and there may be no gross skeletal changes (eight cases in this series).

Hyperparathyroidism with Renal Insufficiency (nephrocalcinosis).—The symptoms are those of Bright's disease (one case in this series).

Acute Parathyroid Poisoning.—This is a condition simulating acute parathyroid poisoning in dogs with sudden death and characteristic pathologic changes (no cases in this series). A case reported by Dawson and Struthers [7] may well fall into this group.

Hyperparathyroidism Simulating (or Complicated by) Paget's Disease.—The existence of this group is not yet certain. There is a discussion of this condition under the section on differential diagnosis (one case in this series).

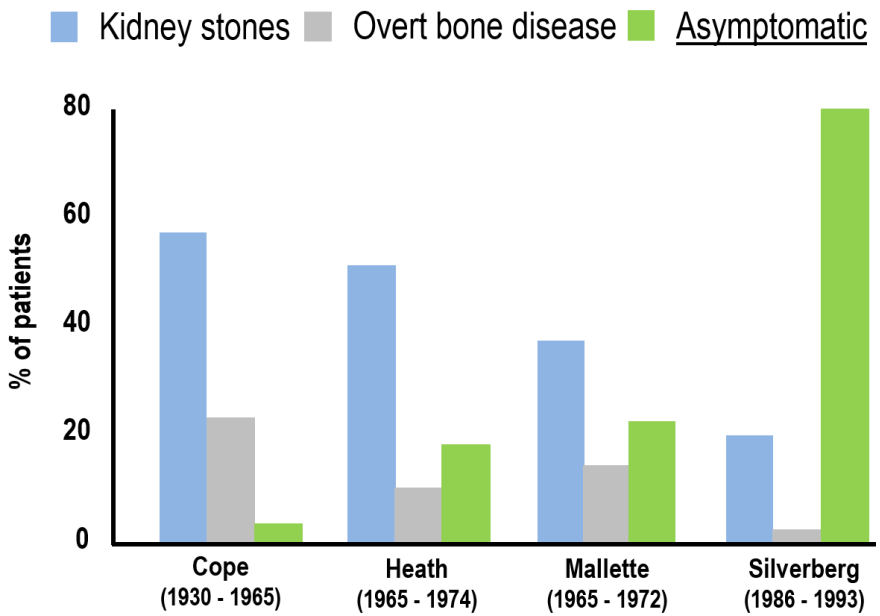


Primary Hyperparathyroidism: changing over time

1920: "Stone, Bone and Abdominal groan"

↓

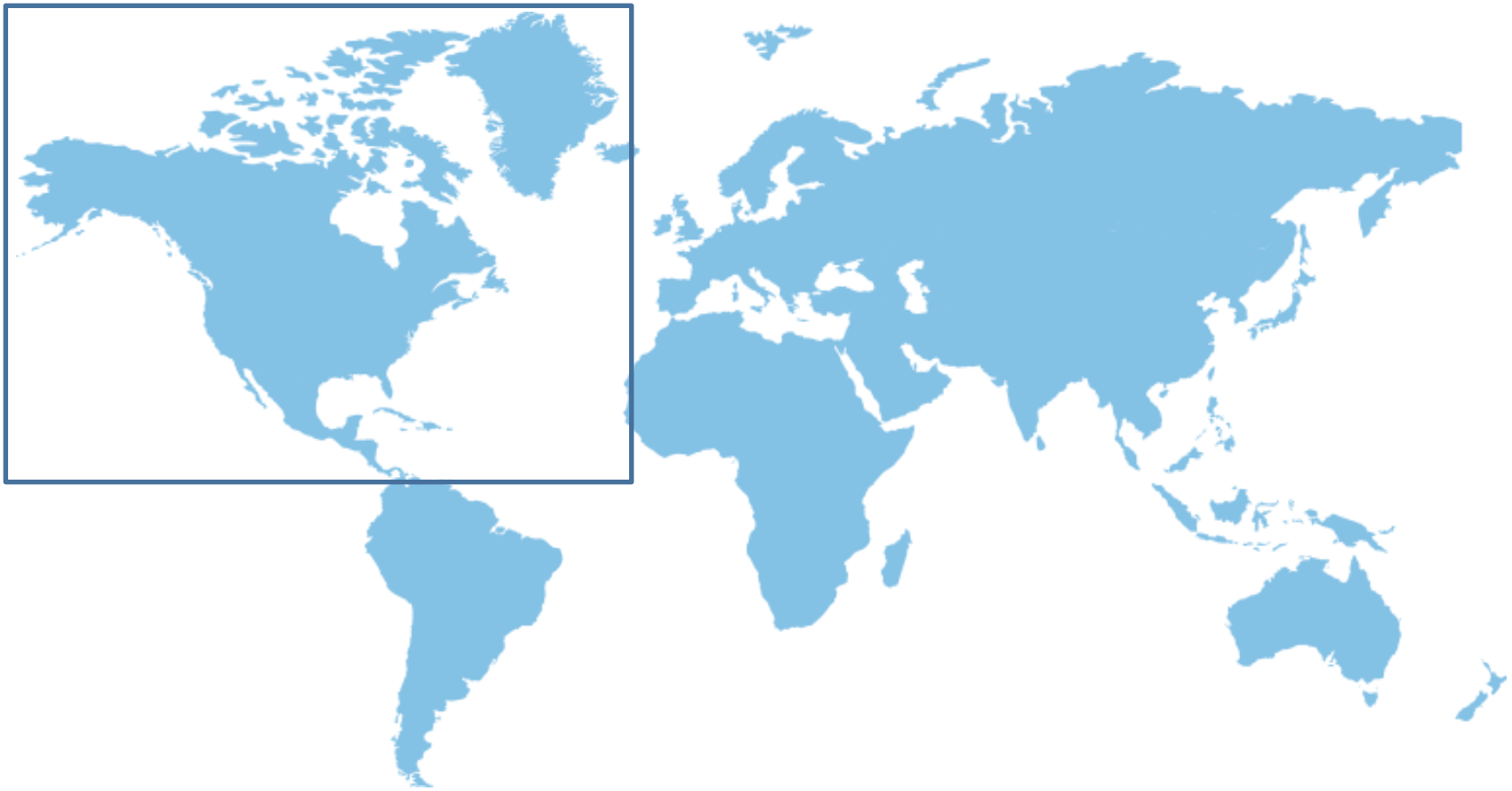
Asymptomatic disease



→ ***"Mild" PHPT***

→ ***Normocalcemic PHPT***

Epidemiology: North America



Epidemiology of Primary Hyperparathyroidism

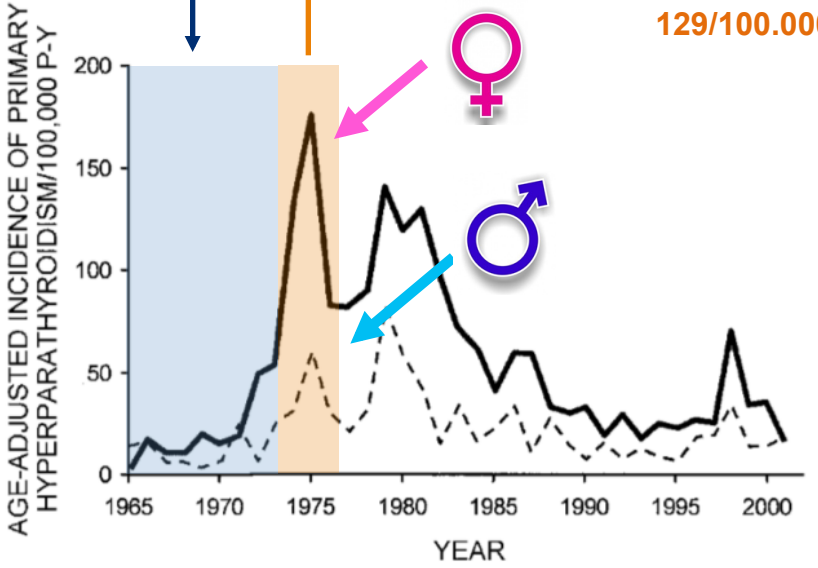
JOURNAL OF BONE AND MINERAL RESEARCH
Volume 21, Number 1, 2006
Published online on September 19, 2005; doi: 10.1359/JBMR.050910

Incidence of Primary Hyperparathyroidism in Rochester, Minnesota, 1993–2001: An Update on the Changing Epidemiology of the Disease

Robert A Wermers,[1] Sundeep Khosla,[1] Elizabeth J Atkinson,[2] Sara J Achenbach,[2] Ann L Oberg,[2] Clive S Grant,[3] and L Joseph Melton III[1,2]

15.8/100.000

Multiple channel biochemical analyzers: 129/100.000 person/year



Age groups	Men n	Men Incidence	Women n	Women Incidence	Both sexes n	Both sexes Incidence
1965 to June 1974						
<45	11	6.6	9	4.8	20	5.6
45–54	4	19.4	8	34.0	12	27.2
55–64	1	6.5	15	70.4	16	43.6
65–74	2	20.4	9	53.5	11	41.3
>75	0	0.0	6	42.5	6	29.3
Total	18	9.0*	47	21.4*	65	15.8†
July 1975–1982						
<45	29	17.6	36	19.7	65	18.7
45–54	10	49.0	54	244.4	64	150.6
55–64	18	111.2	70	354.7	88	244.9
65–74	13	132.3	56	327.2	69	256.1
>75	3	44.8	24	198.5	37	155.3
Total	73	41.3*	250	118.6*	323	82.5†
1983–1992						
<45	24	10.4	23	9.5	47	10.0
45–54	8	26.5	30	93.5	38	61.0
55–64	8	36.1	34	135.1	42	88.7
65–74	5	33.2	18	82.7	23	62.5
>75	0	0.0	10	38.0	10	27.4
Total	45	16.1*	115	40.8*	160	29.1†
1993–2001						
<45	19	7.7	15	6.0	34	6.8
45–54	11	27.3	22	50.2	33	39.2
55–64	5	19.9	21	72.4	26	48.0
65–74	3	17.3	22	98.9	25	63.2
>75	4	29.2	14	47.7	18	41.8
Total	42	13.8*	94	28.4*	136	21.6†

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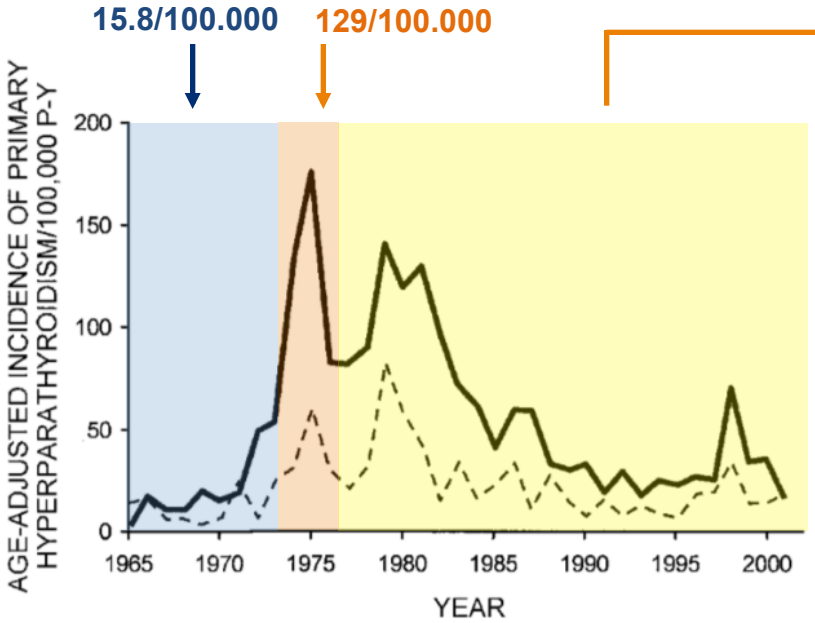


Decline in incidence: 21.6/100.000

- Discontinuation routine chemistry
- Waning neck radiation treatments
- Decreasing exposure to nuclear fallout
- Increased used of hormone therapy
- Increased dietary and supplemental calcium and vitamin D

Epidemiology of Primary Hyperparathyroidism

Kaiser Permanent Southern California database

- 13779 patients
- Racially mixed population
- Incidence and prevalence data

Incidence and Prevalence of Primary Hyperparathyroidism in a Racially Mixed Population

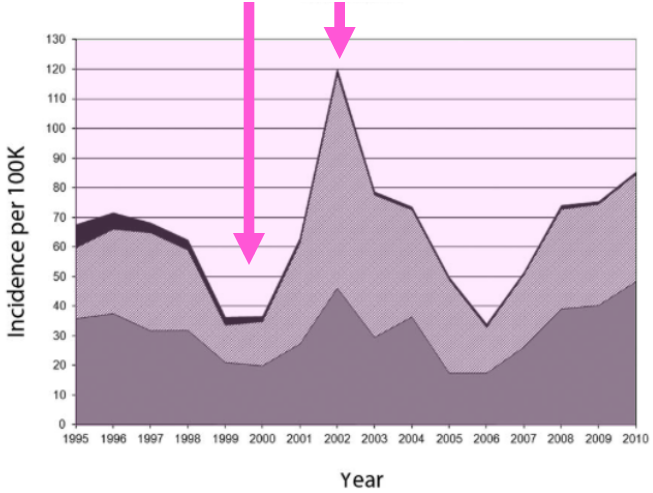
Michael W. Yeh, Philip H. G. Ituarte, Hui Cynthia Zhou, Stacie Nishimoto, In-Lu Amy Liu, Avital Harari, Philip I. Haigh, and Annette L. Adams

J Clin Endocrinol Metab, March 2013, 98(3):1122–1129

36.3-120.2/100.000

13.4-35.6/100.000

Blacks (92/46)
Whites (81/29)
Asians (52/28)
Hispanics (49/17)



Age-adjusted **incidence** of primary hyperparathyroidism by year for women and men

Epidemiology of Primary Hyperparathyroidism

Roma, 9-12 novembre 2017

Incidence and Prevalence of Primary Hyperparathyroidism in a Racially Mixed Population

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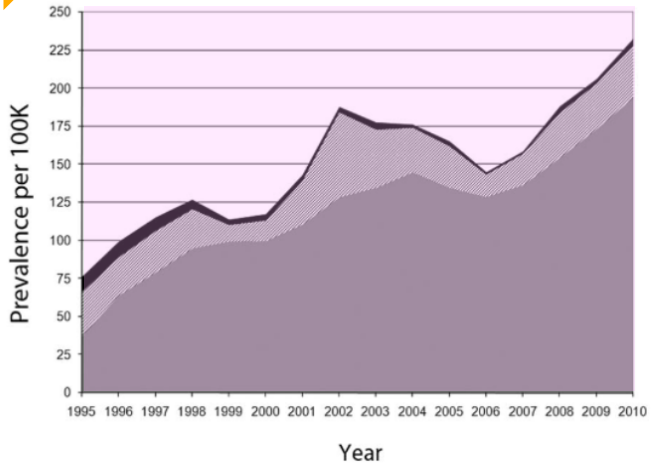
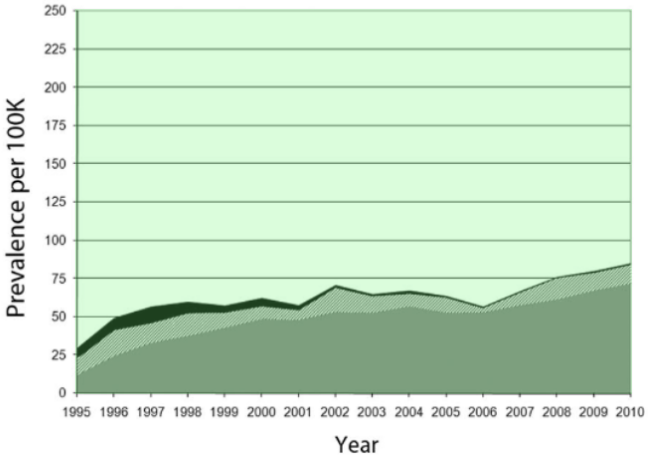
1995-2010

3 fold increased prevalence

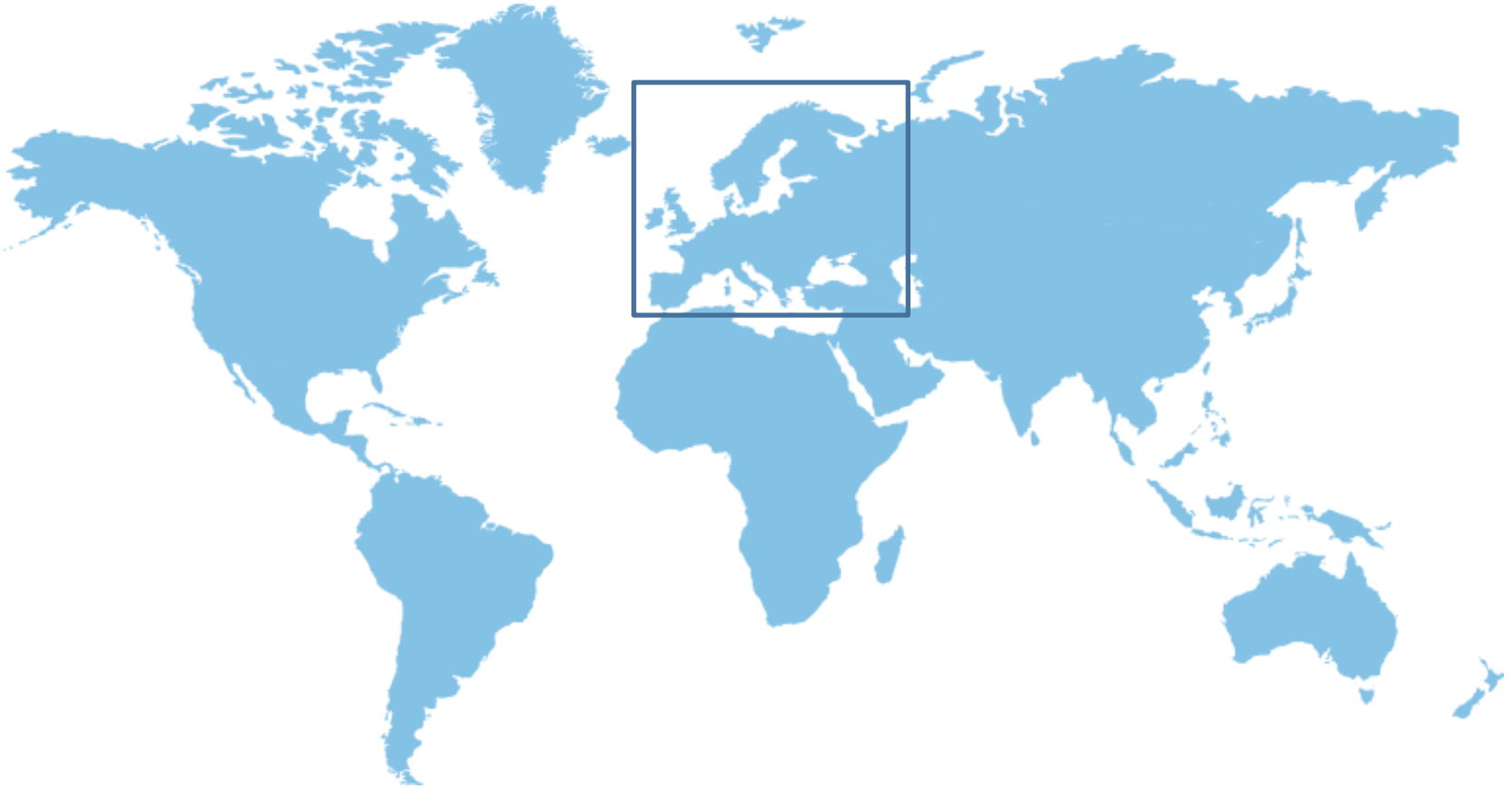
2.89 fold increased prevalence





Age-adjusted **prevalence** of primary hyperparathyroidism by year for women and men

Epidemiology: Europe



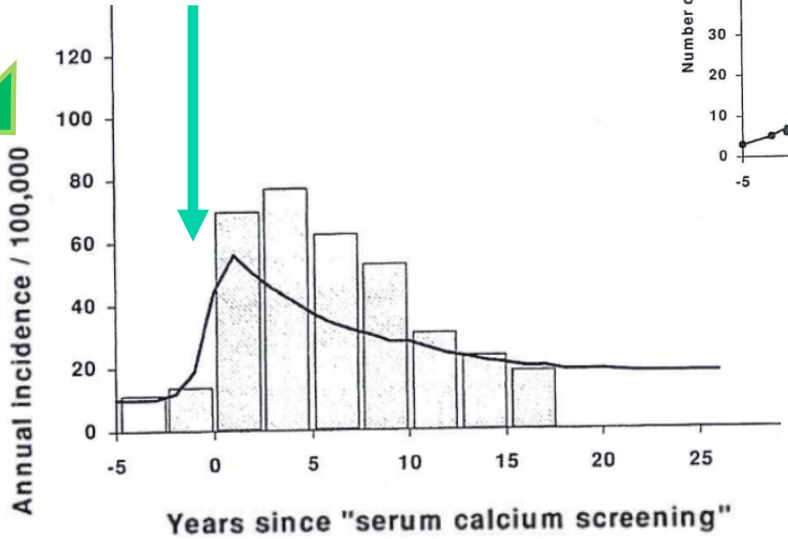
Epidemiology of Primary Hyperparathyroidism in Europe

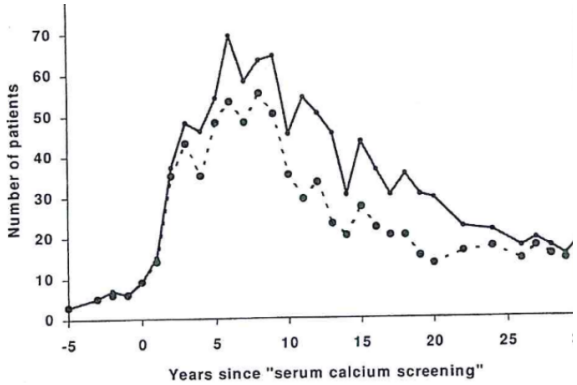
Peak incidence 78/100.00 in 1973-1976
Adami et al. 2002

"CATCH-UP EFFECT"

1971-1974

1976-2001





Epidemiology of Primary Hyperparathyroidism in Europe

1997-2006

Clinical Endocrinology (2009) 71, 485–493

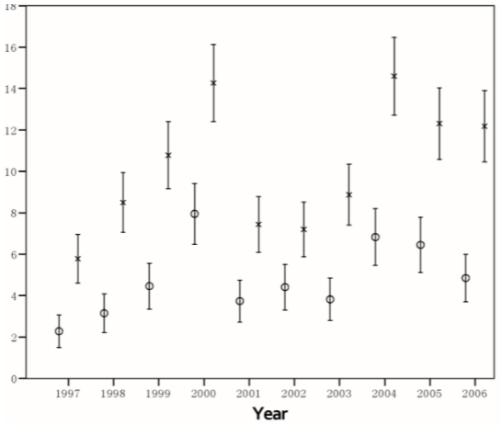
doi: 10.1111/j.1365-2265.2008.03520.x

ORIGINAL ARTICLE

Epidemiology of primary hyperparathyroidism in Tayside, Scotland, UK

Ning Yu*, Peter T. Donnan*, Michael J. Murphy† and Graham P. Leese‡

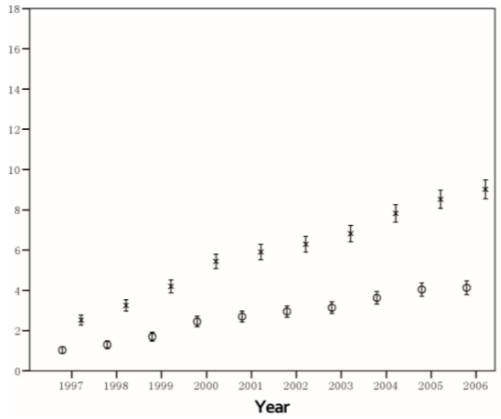
INCIDENCE RATE (n/10.000/year)



M

F

PREVALENCE RATE n/1000



Retrospective electronic database inquiry of serum calcium results and medical record diagnoses

Incidence rate of 57.8 to 142.7 per 100,000 person-years in women and 22.8–79.5 in men (overall, 41.3–113.0 per 100,000 person-years)

Epidemiology of Primary Hyperparathyroidism in Europe

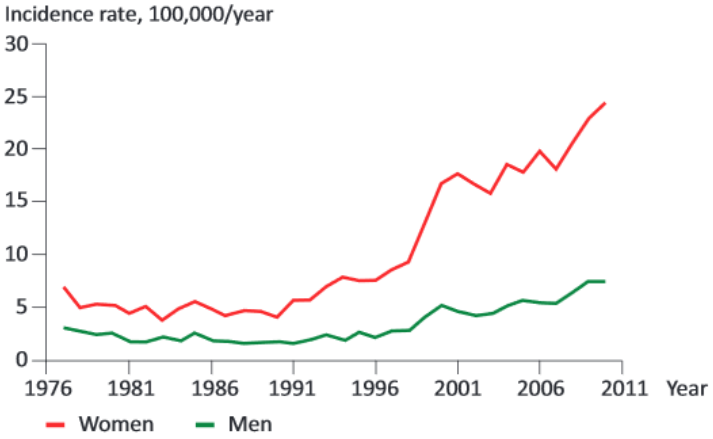
Roma, 9-12 novembre 2017

Dan Med J 60/2 | February 2013 DANISH MEDICAL JOURNAL

1977-2011

Increasing incidence of primary hyperparathyroidism in Denmark

Ali Abood & Peter Vestergaard



- Retrospective electronic record study (all patients with PHPT code) diagnosis
- Progressive rise in incidence rates
- The largest increase in incidence occurred among women more than 50 years of age

Epidemiology of Primary Hyperparathyroidism in Italy

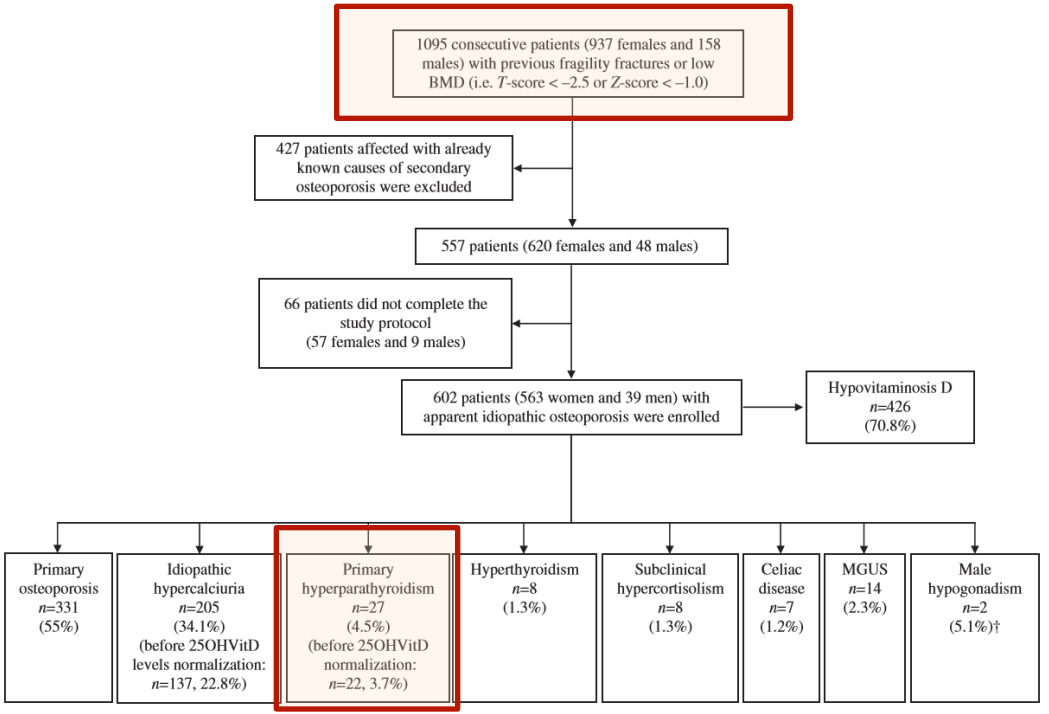
Secondary Osteoporosis in Men and Women: Clinical Challenge of an Unresolved Issue

Disorder	Men,	Women,	p
Drug-induced osteoporosis	28.5 (8)	32.5 (14)	NS
Primary hyperparathyroidism	7.1 (2)	34.8 (15)	< 0.01
Gastrointestinal diseases	10.7 (3)	16.2 (7)	NS
Hypercalciuria	14.2 (4)	0	< 0.01
Hypogonadism/amenorrhea	14.2 (4)	2.3 (1)	NS
Subclinical hypercortisolism	7.1 (2)	0	NS
Hyperthyroidism	0	6.9 (3)	NS
Rheumatoid arthritis and other autoimmune diseases	7.1 (2)	0	NS
Hematological disease	3.5 (1)	4.6 (2)	NS
Osteomalacia	0	2.3 (1)	NS
Alcohol consumption 3 or more units daily	7.1 (2)	0	NS

Prevalence of PHPT of 15 out of 286 women (5.2%) and 2 out of 143 men (1.4%) based upon referrals to the Metabolic Bone Disease Unit in Rome, Italy, from 2007 to 2009

Romagnoli et. al. The Journal of Reumatology 2011

Prevalence of subclinical contributors to low bone mineral density and/or fragility fracture



A 4.5% prevalence of PHPT was observed among 1095 patients consecutively admitted for reduced bone mineral density (BMD) and/or for history of fragility fracture

Eller-Vainicher et. al. EJE 2013

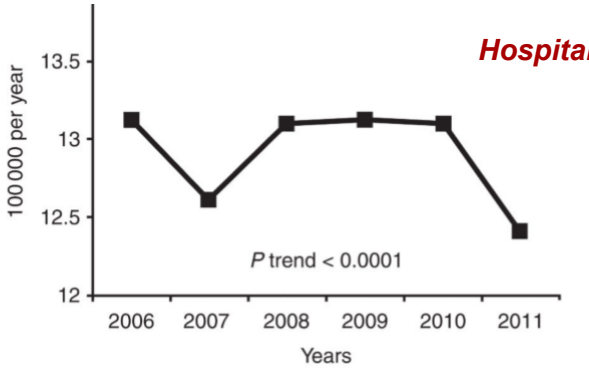
Epidemiology of Primary Hyperparathyroidism in Italy

ITALIAN CHAPTER

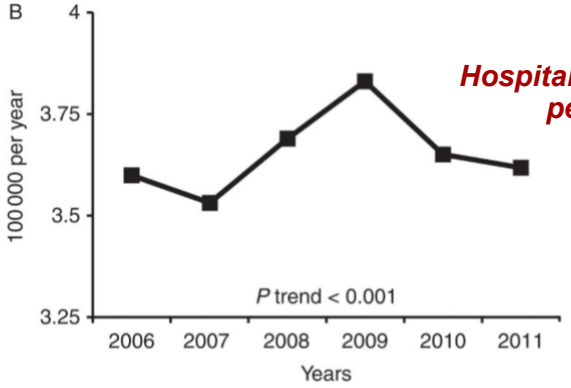
Hospital care for primary hyperparathyroidism in Italy: a 6-year register-based study

- *46 275 hospitalization episodes (2006-2011)*
- *69% in women and 31% in men*
- *Mean age 63.3±39.8 years*
  Patients' mean age significantly increased during the years
- *Mean length of stay 8.2±10.5 days*
- *Admissions for surgical procedures 26.9% of the total hospitalizations*
- *Decrease in the frequency of hospitalization and increase of surgery rate*

Cipriani et al. EJE 2015



Hospitalization rate for PHPT/100 000 per year in Italy



Hospitalization rate for PHPT SURGERY per 100 000 per year in Italy

Epidemiology of Primary Hyperparathyroidism in Italy

ITALIAN CHAPTER

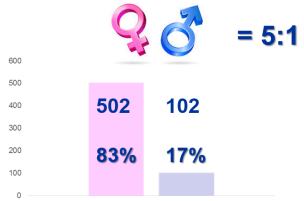
Progetto "Epidemiologia dell' Iperparatiroidismo Primario in Italia"

Totale Centri 62 – 1927 pazienti

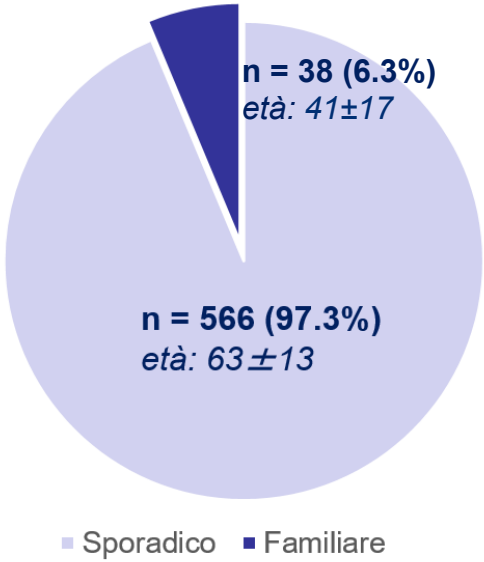
- **1323 Follow-up**
- **604 Nuove diagnosi**
  - **345 Follow-up**

Età media: 61±14 (15-88) anni

Distribuzione per sesso



Eziopatogenesi



23 MEN1
6 FIHP
3 HPT-JT
6 FHH

Saponaro et al. unpublished

Gender distribution

TABLE 1. CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF ROCHESTER, MN, RESIDENTS WHO RECEIVED A DIAGNOSIS OF DEFINITE OR POSSIBLE PRIMARY HYPERPARATHYROIDISM IN 1965–2001

Characterisitic	Time period: 1965 to June 1974 (n = 65)	July 1974–1982 (n = 323)	1983–1992 (n = 160)	1993–2001 (n = 136)
Mode of diagnosis, *n* (%)				
Histologic evidence	23 (35.4)	86 (26.6)	30 (18.8)	37 (27.2)
Inappropriate PTH level	27 (41.5)	145 (44.9)	63 (39.4)	53 (39.0)
Hypercalcemia > 1 year	13 (20.0)	75 (23.2)	44 (27.5)	36 (26.5)
Possible	2 (3.1)	17 (5.3)	23 (14.4)	10 (7.4)
Sex, *n* (%)				
Female		250 (77.4)	115 (71.9)	94 (69.1)
Male		73 (22.6)	45 (28.1)	42 (30.9)
Age (years)				
Mean ± SD		56.4 ± 16.4	52.5 ± 16.2	56.1 ± 16.2
Presentation,				
Symptom		24 (7.4)	5 (3.1	
Abnormal serum calcium	50 (76.9)	295 (91.3)	153 (95.	
Other biochemical or radiologic abnormality	1 (1.5)	1 (0.3)	2 (1.3	
Autopsy	0 (0)	3 (0.9)	0 (0)	
Uncertain	1 (1.5)	0 (0)	0 (0)	
Maximum serum calcium level (mg/dl)				
Mean ± SD	10.9 ± 0.5	10.9 ± 0.6	10.7 ± 0	
Initial management, *n* (%)				
Surgery ≤6 months after diagnosis	18 (27.7)	67 (20.7)	21 (13.	
Surgery recommended but refused	6 (9.2)	10 (3.1)	3 (1.9	
Surgery recommended but patient too ill	2 (3.1)	14 (4.3)	1 (0.6	
Decision to observe	37 (56.9)	232 (71.8)	135 (84.	
Uncertain	2 (3.1)	0 (0)	0 (0)	

Mean F:M=2:1 (peak '80 3.4:1)
Mean age 52-56 yrs
Sympt: 20% - 5%

Wermers, R. A. et. al. JBMR 2006

	N (%)	Age, Mean (SD)
Classic PHPT		
Total	6868 (100.0)	64.0 (13.4)
Gender		
Women	5311 (77.3)	64.7 (12.8)
Men	1,557 (22.7)	61.9 (14.8)
Race		
Asian	335	
Black	1191	
Hispanic	1054 (15.3)	58.9 (14.2)
Other	415 (6.1)	61.0 (13.4)
White	3873 (56.4)	66.0 (12.9)

F:M= 3.4:1

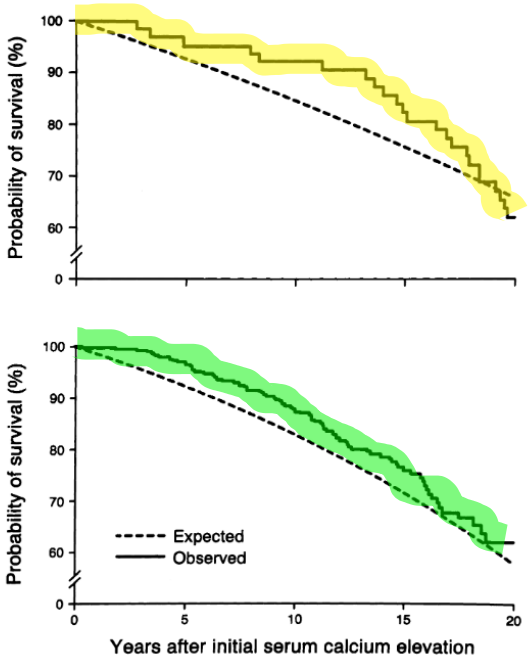
Yeh M.W. et. al. JCEM 2013

	Whole series (n = 417)	Males (n = 93)	Females (n= 324)	p
Age (years)	61.0 ± 13.2	58.6 ± 14.5	61.7 ± 12.8	**0.046**
BMI (kg/m²)	25.3 ± 5	25.7 ± 4.5	25.1 ± 5.2	0.31
Symptomatic (n, %)	210 (50.4%)	58 (62.3%)	152 (47%)	**0.016**
PTH (ng/L)	135.9 [134.5]	121 [148]	138 [130]	0.783
Total serum calcium (mg/dL)	11.2 ± 1.1	11.2 ± 1.2	11.2 ± 1.1	0.654
Ionized calcium (mmol/L)	1.45 ± 0.2	1.5 ± 0.2	1.4 ± 0.2	0.337
25OH vitamin D (µg/L)	28			
Vitamin D deficiency (%)				
Urinary calcium (mg/24h)	257			
Serum Phosphate (mg/dL)	2.			
eGFR (mL/min/1.73 m²)	79			
Presence of kidney stones (n, %)	15			
Presence of osteitis fibrosa cystica (n, %)	87 (20.9%)	20 (21.5%)	67 (20.7%)	0.977
Distal third radius T score	-2.3 ± 1.6	-1.9 ± 1.4	-2.4 ± 1.7	**0.001**
Lumbar spine T score	-2.4 ± 1.5	-1.7 ± 1.5	-2.6 ± 1.4	**0.001**
Femoral neck T score	-2.0 ± 1.2	-1.8 ± 1.3	-2.1 ± 1.2	**0.013**
Osteoporosis at any site (n, %)	202 (48.4%)	33 (35.5%)	169 (52.2%)	**0.0066**
Positive pre-surgical localization (n, %)				

Mean F:M= 3.5:1
Mean age 61±13.2 yrs
Sympt: 50.4%

Castellano E. et. al. JCEM 2017

Mortality of Primary Hyperparathyroidism



Survival after the Diagnosis of Hyperparathyroidism: A Population-based Study*

Robert A. Wermers, MD, Sundeep Khosla, MD, Elizabeth J. Atkinson, MS, Clive S. Grant, MD, Stephen F. Hodgson, MD, W. Michael O'Fallon, PhD, L. Joseph Melton, III, MD

PRE-SCREENING ERA

Mortality rate of Rochester residents with primary hyperparathyroidism compared with that expected for Minnesota white residents of similar age and gender

POST-SCREENING ERA

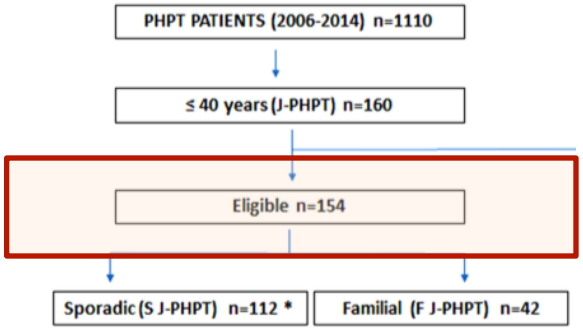
Epidemiology of Juvenile PHPT

PHPT is rare in infants, and uncommon in children and adolescents, with an estimated incidence of 2–5/100,000 person-year, without a gender predilection

Levine et al. JCEM 2014

	Girard 1982(2)	Huang 1993(3)	Cronin 1996(4)	Lawson 1996(5)	Loh 1998(6)	Harman 1999(7)	Hsu 2002(8)	Kollars 2005(9)	Venail 2007(10)	Mallet 2008(11)	Bhadada 2008(12)	George 2010(13)	Durkin 2010 (14, 15)	Li et al.(16)	Summary Proportion (percentage), or Mean, *n*
Sex distribution															
Males	40/69	NA	5/8	NA	5/7	NA	6/11	NA	1/4	26/44	6/14	4/18	3/12	5/12	101/199 (51%)
Females	20/69	NA	3/8	NA	2/7	NA	5/11	NA	3/4	18/44	8/14	14/18	9/12	7/12	98/199 (49%)
Clinical signs and symptoms															
Kidney stones	NA	20/74	NA	7/11	1/7	14/33	7/11	21/52	0/4	18/44	7/14	6/18	NA	9/12	110/280 (39%)
Hypercalciuria	NA	39/74	NA	NA	NA	NA	9/10	NA	NA	32/44	NA	NA	NA	NA	80/134 (60%)
Bone disease	NA	33/74	NA	7/11	NA	9/33	2/7	18/52	4/4	7/44	10/14	16/18	NA	11/12	117/269 (43%)
Abdominal pain/vomiting	NA	3/74	7/8	NA	2/7	NA	NA	15/52	3/4	2/44	NA	NA	NA	4/12	32/189 (17%)
Hypertension	NA	6/74	NA	NA	1/7	NA	NA	NA	NA	NA	NA	NA	NA	1/12	8/93 (9%)
Vague symptoms	NA	NA	NA	10/11	3/7	7/33	1/11	NA	NA	8/44	NA	NA	NA	6/12	49/140 (35%)
Hypercalcemic crisis	NA	NA	4/8	NA	NA	NA	NA	NA	0/4	1/44	NA	NA	NA	1/12	6/68 (9%)
Asymptomatic	NA	NA	1/8 (MEN2a)	1/11	NA	6/33 (18%)	2/11 (18%)	11/52	0/4	8/44	1/14 (MEN1)	NA	NA	0/12	29/211 (14%)

Epidemiology of Juvenile PHPT



	Whole group ($n = 154$)	Normal range	Sporadic ($n = 112$)	Familial ($n = 42$)	P
Sex (F:M)	2.8:1	–	3.6:1	1.6:1	$P = 0.036$
Age at diagnosis (years)	32 ± 7	–	33.3 ± 7	29 ± 8	0.001
Serum calcium (mg/dL)	10.9 ± 1	8.6–10.2	11 ± 0.9	10.9 ± 1.1	0.3
Serum albumin adjusted calcium (mg/dL)	10.6 ± 1	8.6–10.2	10.6 ± 1.1	10.6 ± 1.2	0.7
Ionized serum calcium (mmol/L)	1.50 ± 0.1	1.13–1.32	1.49 ± 0.13	1.50 ± 0.16	0.8
Serum phosphate (mg/dL)	2.4 ± 0.56	2.7–4.5	2.4 ± 0.54	2.5 ± 0.61	0.3
Plasma intact PTH (pg/mL)	111 (78–171)	15–75	118 (80–174)	97 (71–161)	0.05
Serum 25OHD (ng/mL)	19.6 ± 10	30–100	17.7 ± 9.8	21.7 ± 12.4	0.2
Serum osteocalcin (ng/mL)	32.5 ± 25.2	6.8–34	33.2 ± 27.5	30.9 ± 19.1	0.9
Serum BSAP (μg/L)	23.2 ± 15.8	2–20	23.8 ± 16.2	21.9 ± 14.9	0.2
24-h Urinary calcium (mg/24 h)	376.7 ± 154	<300	372.2 ± 156.4	401.3 ± 230	0.2
Lumbar spine		–			
BMD (g/cm²)	0.93 ± 0.18		0.93 ± 0.18	$0.94 \pm .17$	0.4
z-score	-1.08 ± 1.16		-1.06 ± 1.16^{a}	-0.85 ± 1.26^{a}	0.4
Femoral neck		–			
BMD (g/cm²)	0.74 ± 0.12		0.73 ± 0.17	0.78 ± 0.13	0.5
z-score	-0.98 ± 0.95		-1.02 ± 0.96	-0.87 ± 0.93	0.4
One-third distal radius		–			
BMD (g/cm²)	0.66 ± 0.19		0.67 ± 0.14	0.62 ± 0.23	0.6
z-score	-0.84 ± 1.31		-0.71 ± 1.34	-1.18 ± 1.27	0.07
Nephrolithiasis n (%)	77 (50%)	–	62 (55%)	15 (35.7%)	0.005
Clinical fractures n (%)	7 (4.5%)	–	4 (3.5%)	3 (2.6%)	0.5
Neuropsychiatric symptoms n (%)	49 (31.8%)	–	41 (36.6%)	8 (19%)	0.04
Low BMD (%)	27 (17.5%)	–	21 (18.7%)	6 (14.2%)	0.5

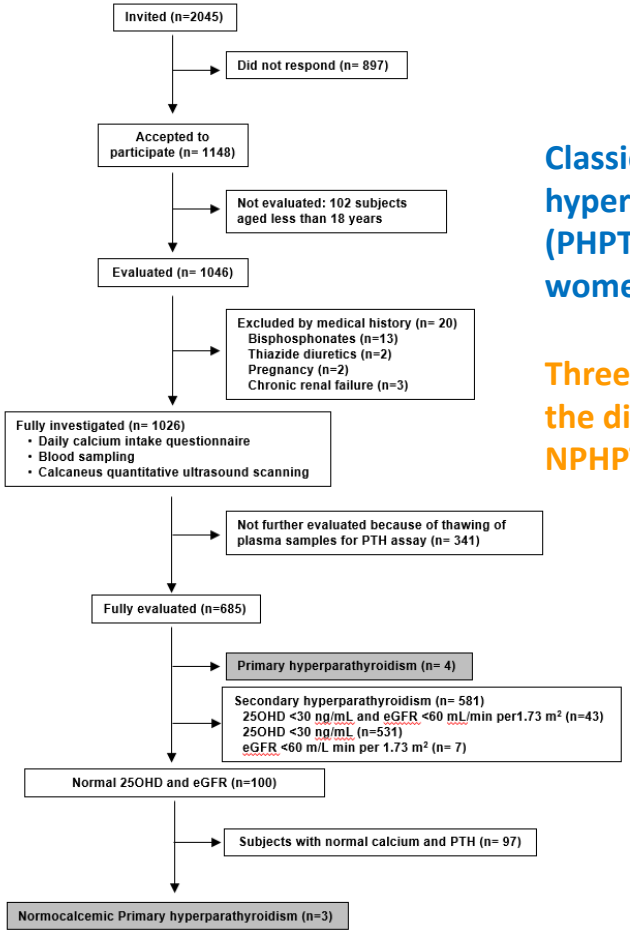
Saponaro et al. Endocrine 2017

Normocalcemic Primary Hyperparathyroidism (NPHPT)

OUR EXPERIENCE

Normocalcemic primary hyperparathyroidism: a survey in a small village of Southern Italy

E Vignali, C Marcocci et al.



Classical primary hyperparathyroidism (PHPT) was diagnosed in 4 women (0.58%).

Three males (0.44 %) met the diagnostic criteria of NPHPT.

Take home message

- As the clinical presentation of the disease has evolved over the past decades from the symptomatic variant through the asymptomatic variant and now even to a normocalcemic variant, the epidemiology of PHPT has undergone profound changes.

- These studies have shown that the incidence of the disease is closely related to the frequency of routinely obtained biochemical screening tests, socioeconomic issues (i.e. low vitamin D status), dietary habits (i.e. calcium and vitamin D supplementation), as well as the degree of awareness among physicians.

- These varying presentations are associated with different and country-specific epidemiological patterns.

RINGRAZIAMENTI

Prof. Claudio Marcocci
Dott. ssa Filomena Cetani

GRAZIE PER L'ATTENZIONE !