Increasing incidence of primary hyperparathyroidism in Denmark

Ali Abood & Peter Vestergaard

ABSTRACT

INTRODUCTION: Primary hyperparathyroidism is a common endocrine disorder with different epidemiological patterns among countries. In Denmark, the incidence of primary hyperparathyroidism was last described in 1999 when it was reported to follow an increasing trend. In the present study, we evaluated trends in the incidence of primary hyperparathyroidism in Denmark up to 2010.

MATERIAL AND METHODS: All patients diagnosed with primary hyperparathyroidism from 1977 to 2010 were included. Annual incidence rates were calculated.

RESULTS: The overall incidence was clearly increased at the end of 2010 with an annual rate of 16 per 100,000. Following a cyclic curve, year-to-year incidence rates were fluctuating. During the entire period, the incidence was higher in women than in men. Furthermore, in women above the age of 50 years, a five-fold increase in incidence was observed, while there was no difference in the increase among men above the age of 50 years compared with men under the age of 50 years.

CONCLUSION: The incidence of primary hyperparathyroidism in Denmark continues its remarkable rise. The overall increase in incidence may be the result of more frequent plasma calcium measurements as well as the prevailing obesity epidemic. The dramatic increase in incidence observed among women over the age 50 years requires further studies. The causes of the cyclic trend observed are uncertain, as no seasonal variation was seen.

FUNDING: not relevant.

TRIAL REGISTRATION: not relevant.

Primary hyperparathyroidism (PHPT) is a common endocrine disorder. Over the past years, PHPT has experienced a dramatic change in epidemiology. The disease is often asymptomatic; hence, its incidence was previously often underestimated. With the increasing availability of plasma calcium measurements during the 1970s, the incidence of PHPT has risen significantly. In 1974, this resulted in the hitherto highest reported US incidence of 129 cases per 100,000 person-years [1]. In subsequent years, a significant decline in the US incidence of PHPT was seen. This was probably owed to the fact that the majority of prevalent cases had been detected prior to 1974, and after this point in time the incidence thus represented actual incident cases [2]. The latest available figures from the US show a continuing downward trend in incidence with an overall incidence rate of 21.6 per 100,000 person-years in the 1993-2001 period [1]. This downward trend was not observed in Denmark – in contrast, the incidence in Denmark was increasing. From 1980 to 1999, the incidence rose significantly among women (from 3.4 to 5.8 per 100,000 per year), while the increase for men was less pronounced [3]. It is worth noting that the large difference in incidence rates between Denmark and the United States probably reflects a large pool of undetected cases in Denmark. Similarly, in Switzerland, the incidence of parathyroidectomies was 3.8 per 100,000 per year between 2000 and 2004, i.e. low compared with the US [4]. There are thus considerable geographical differences, which underlines the importance of unknown aetiologic factors. This is also supported by a Scottish study on the incidence of PHPT in the 1997-2006 period, which reported a fluctuating and cyclical pattern [5]. In the Scottish study, the incidence was reported to have increased if annual incidence rates from 1997 and 2006, respectively, were compared. When comparing year-to-year incidence rates within the 1997-2006 period, large fluctuations were observed. Furthermore, unknown aetiologic factors were suggested as possible explanations [5]. The variations in the epidemiology of PHPT may, in part, be attributed to temporal components, but geographical/aetiologic factors also seem to play a role. These are not well documented and need to be clarified.

The incidence of PHPT in Denmark has not been assessed since 1999 [3]. The purpose of the present study was to evaluate incidence rates of PHPT in the 2000-2010 period to determine if the development in Denmark is similar to that seen in the rest of the world.

MATERIAL AND METHODS

Included were all patients who were registered in the National Hospital Discharge Register (Sundhedsstyrelsens Landspatientregister) [6] from 1977 to 2010 with a PHPT diagnosis. International Classification of Diseases (ICD) 8-codes: 252.00 (hyperparathyroidismus primarius, adenoma), 252.01 (hyperparathyroidismus primarius, hyperplasia), 252.03 (crisis hyperparathyroidismi), 252.04 (osteitis fibrosa cystica generalisata), 252.05 (nephrocalcinosis e hyperparathyroidismi), 252.08

ORIGINAL ARTICLE

Institute for Medicine and Health Technology, Aalborg University

Dan Med J 2013;60(2):A4567

FIGURE 1

Incidence of primary hyperparathyroidism among men and women from 1977 to 2010 in Denmark expressed as crude incidence rates per 100,000 per year.

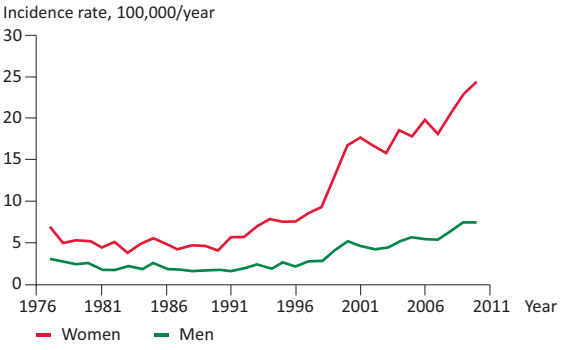


FIGURE 2

Age-stratified incidence of primary hyperparathyroidism among men and women from 1980 to 2010 in Denmark expressed as crude incidence rates per 100,000 per year.

TABLE 1

Number of confirmed diagnoses and median age at time of diagnosis in the 1977-2010 period for men and women.

	Women		Men		
	n	age, years, mean ± SEM	n	age, years, mean ± SEM	p-value
1977	178	49.4 ± 2.0	77	42.6 ± 2.8	0.06
1978	128	54.0 ± 2.2	68	50.5 ± 2.6	0.31
1979	137	53.8 ± 2.2	61	52.0 ± 2.7	0.64
1980	134	53.9 ± 2.1	65	46.2 ± 2.8	0.03
1981	115	54.5 ± 2.2	44	51.0 ± 3.1	0.38
1982	132	57.9 ± 1.7	43	51.3 ± 3.3	0.06
1983	98	57.1 ± 2.2	56	54.3 ± 2.5	0.43
1984	126	55.5 ± 2.2	46	54.6 ± 2.5	0.82
1985	144	58.0 ± 1.8	65	54.4 ± 2.1	0.24
1986	126	61.4 ± 1.5	46	48.9 ± 3.2	< 0.01
1987	109	62.5 ± 1.5	45	52.1 ± 2.7	< 0.01
1988	122	59.7 ± 1.5	40	52.8 ± 2.6	0.02
1989	120	64.4 ± 1.4	42	51.0 ± 3.0	< 0.01
1990	106	64.6 ± 1.5	44	56.6 ± 2.6	< 0.01
1991	148	65.2 ± 1.1	40	62.2 ± 2.2	0.23
1992	149	62.2 ± 1.4	49	58.2 ± 2.6	0.16
1993	183	62.6 ± 1.2	55	52.8 ± 3.2	< 0.01
1994	207	61.4 ± 1.2	48	56.7 ± 2.5	0.10
1995	199	65.2 ± 1.1	68	59.5 ± 2.0	< 0.01
1996	201	63.6 ± 1.1	55	62.7 ± 2.3	0.72
1997	229	63.8 ± 1.0	72	61.0 ± 2.0	0.19
1998	249	66.9 ± 1.0	71	57.1 ± 1.9	< 0.01
1999	349	63.6 ± 0.8	107	57.5 ± 2.0	< 0.01
2000	451	65.2 ± 0.7	130	62.6 ± 1.4	0.09
2001	478	65.0 ± 0.7	122	62.1 ± 1.5	0.07
2002	453	65.1 ± 0.7	111	60.4 ± 1.6	< 0.01
2003	430	65.0 ± 0.7	118	61.2 ± 1.6	0.02
2004	506	63.4 ± 0.7	137	59.4 ± 1.5	0.01
2005	487	64.7 ± 0.7	152	62.4 ± 1.3	0.11
2006	543	66.3 ± 0.6	146	62.5 ± 1.3	< 0.01
2007	498	63.4 ± 0.7	145	60.5 ± 1.4	0.06
2008	569	64.0 ± 0.6	174	61.3 ± 1.2	0.04
2009	637	65.2 ± 0.6	205	63.0 ± 1.1	0.07
2010	681	63.7 ± 0.6	207	60.6 ± 1.2	0.01

SEM = standard error of the mean.

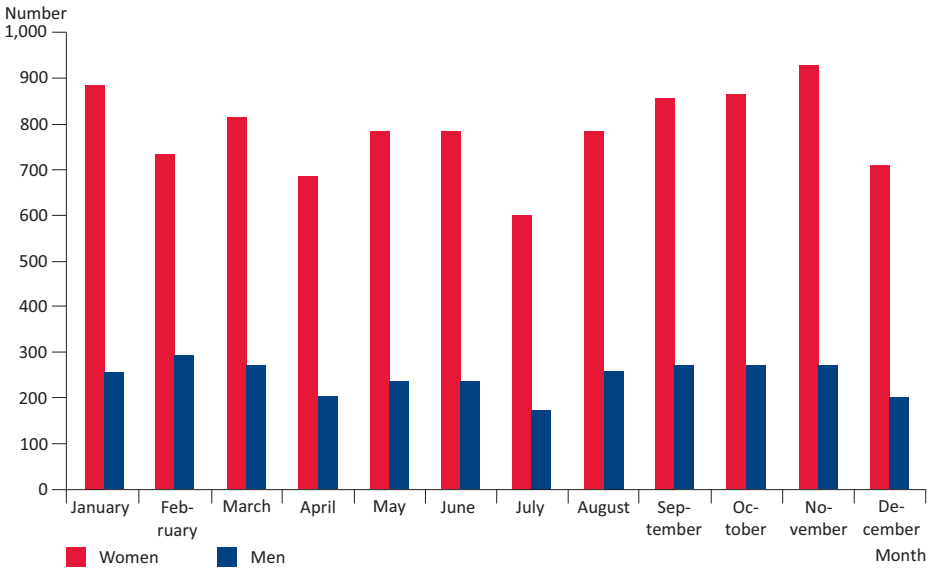
(hyperparathyroidismus alia), 252.09 (hyperparathyroidismus), and ICD10 codes: E21.0 (primary hyperparathyroidism), E21.2 (secondary hyperparathyroidism), E21.3 (hyperparathyroidism without specification). The ICD 8 code system was used between 1977 and 1993, while the ICD 10 code system was applied from 1994 to 2010. Before 1990, only admissions were reported, but from 1990 to 1994 some departments started including reports from outpatient clinics and emergency rooms. From 1995 reports from all outpatient clinics and emergency rooms were included. It was determined when a diagnosis was initially confirmed and all patients who were diagnosed between 1977 and 2010 were included in the analysis. Incidence rates were calculated as the number of people with newly diagnosed PHPT in a given year divided by the population as per 1 January in that year obtained from Statistics Denmark (Danmarks Statistik, Statistikbanken). The mean and standard error of the mean (SEM) were used as the descriptive statistics, and t-tests for the two groups were used for statistical testing. All calculations were performed using SPSS for Windows 19 (IBM).

Trial registration: not relevant.

RESULTS

Figure 1 shows the crude incidence rates of PHPT among men and women in the 1977-2010 period in Denmark. Throughout the whole period, incidence rates were higher among women than among men. Until about 1998, incidence rates among men remained relatively

FIGURE 3



Seasonal variation in the incidence of primary hyperparathyroidism in the 1977-2010 period.

stable. Subsequently, a 3-fold increase was observed from 1998 to 2010. Among women, the incidence rates remained relatively stable until about 1990 after which year a 5-fold increase was seen from 1990 to 2010. **Table 1** shows the age and sex of newly diagnosed patients with PHPT from 1977 to 2010. As a result of the rapid increase in the number of women with newly diagnosed PHPT the ratio of men versus women was gradually reduced from about 30% men in 1977 to around 23% men in 2010. The average age increased, so that newly diagnosed women were, on average, about 55 years in the 1980s, while they were around 65 years at the end of the period. In the 1980s, the mean age of newly diagnosed men was slightly above 50 years compared with slightly more than 60 years at the end of the period causing an increase in the average age for both men and women by ten years during the study period. **Figure 2** shows the age-specific incidence for men and women. The largest increase occurred among women above 50 years of age, for whom incidence rates experienced a 5-fold increase. Among men aged 50 years or more, incidence rates increased by a factor of three. For women under 50 years of age, a factor three increase was observed, while men under age 50 years also saw a factor three increase.

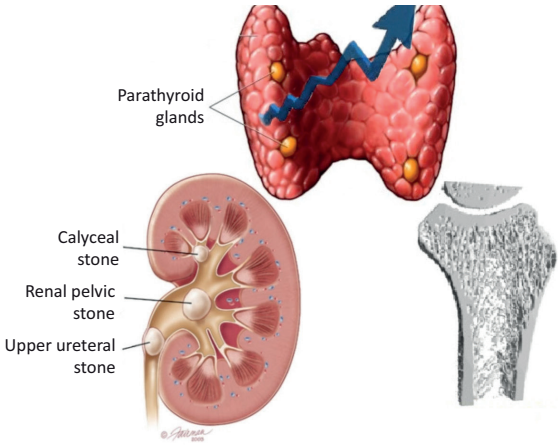
Figure 3 shows the seasonal variation in the incidence of PHPT for the 1977-2010 period. When comparing men and women, no seasonal variation was seen.

DISCUSSION

This study reveals a continuing increase in the incidence rates of PHPT in Denmark during the 2000-2010 period. The increase was seen in both men and women, especially above 50 years of age and it was more pronounced for women. It should be noted that incidence rates were only increasing when the entire period was considered, as the fluctuations in incidence from one year to the next were rather large. A similar pattern was seen in Scotland [5]. In the Scottish study [5], it was suggested that these fluctuations could be season-related, but there are still no studies that definitively confirms this. The reason for these fluctuations thus remains unclear. Unknown aetiologic factors probably play a role [5] and need to be clarified. In our study, there was no seasonal variation. Two months (July and December) had a lower incidence of newly diagnosed cases, but both are holiday months, and a lower activity in the health-care system may explain the lower frequency observed. For example, December was followed by a higher incidence of newly diagnosed cases in January. Among women, there were a few more new cases in the months of September through November than in the months of February through April. However, this could not be seen in men.

The incidence of 21.6 per 100,000 per year seen in the US [1] for the 1993-2001 period is close to but still well above the Danish incidence of 16 per 100,000 per year in 2010 demonstrated in this study. It is thus possible that the incidence will continue to increase in Denmark.

The general upward trend in the incidence of PHPT observed in this study may, in part, be attributed to the fact that more people are diagnosed as a result of more measurements being made. However, this cannot explain the cyclical pattern observed. Another reason for



Primary hyperparathyroidism results in elevated plasma calcium levels as well as more excessive bone resorption, thus contributing to kidney stones, bone demineralization and pathological bone fractures. The incidence of PHPT in Denmark is increasing and may in theory affect the incidence of kidney stones and osteoporosis.

the increasing incidence of PHPT may be the prevailing obesity epidemic [7]. A meta-analysis has shown that on average PHPT patients are heavier than controls [8]. Their greater body weight can lead to resistance to parathyroid hormone (PTH) and resistance to thyroid-stimulating hormone and insulin. Studies have also shown increasing PTH-levels with increasing body weight, possibly due to a declining level of 25-hydroxy-vitamin D, which is fat soluble [9, 10]. It is therefore perhaps possible to develop autonomy in the parathyroid glands and thus PHPT in obese patients. Consequently, with the increasing body weight in the population, a higher rate of PHPT is likely.

It should be underlined that neither the diagnostic criteria of PHPT nor the diagnostic tools have changed during the period evaluated, which makes incidence rates from different years comparable, which is a clear strength of this study.

The clear over-representation of women was also to seen in Scotland [5], Switzerland [4], USA [1] and Denmark before 2000 [3]. It seems probably that part of the explanation may be that women come into contact with the health-care system more frequently and therefore may have their plasma calcium levels measured more often, causing them to be diagnosed more frequently [3].

Oestrogen has an anti-resorptive effect resulting in a lower efflux of calcium from the skeleton, which lowers plasma calcium in primary hyperparathyroidism [11-17]. Another explanation may thus be that the decline in oestrogen levels in women after the menopause can unmask a mild hyperparathyroidism, whereby more women are detected and classified as incident [1]. This hypothesis is supported by the fact that the increase is more pronounced above 50 years of age.

In contrast to the development observed in Denmark and Scotland, the incidence of PHPT in the US is declining [1]. A complete and definitive explanation for this is still pending, but part of the explanation probably lies in a widespread use of therapeutic head/neck radiation in the 1930s and 1940s in the United States. It is known that excessive exposure to head/neck radiation may cause sporadic primary hyperparathyroidism [1, 18, 19]. This may also help explain the dramatic increase in the incidence in 1974. Over time a reduction in the incidence may be expected as the effects of radiation decreases. It should also be noted that when comparing incidence rates before 1974 (15.6 per 100,000 person-years) and from 1993-2001 (21.6 per 100,000 person-years), there is actually an increase in incidence in the US [1]. It should be noted that these numbers are not entirely comparable due to a more limited use of plasma calcium measurements before 1974.

In summary, the increase in incidence observed in Denmark may, in part, be attributed to more measurements being made. In addition, obesity may also play a role. The over-representation of women is, among others, due to the fact that women more often come into contact with the health-care system resulting in an unmasking a mild PHPT, especially after menopause where the antiresorptive properties of oestrogen are lost. The cyclic variations seen in our study are also observed in Scotland, and may be attributed to unknown aetiological factors.

CONCLUSION

A continuing increase was observed in the incidence of primary hyperparathyroidism in Denmark from 2000 to 2010. Part of the increase can be attributed to increased diagnostic activity. A contributing reason for the increase may be the increasing body weight in the population.

CORRESPONDENCE: *Peter Vestergaard,* Medicinsk-endokrinologisk Afdeling, Aalborg Universitetshospital, Hobrovej 18-22, 9100 Aalborg, Denmark.

ACCEPTED: November 8 2012

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedbul.dk.

LITERATURE

1. Wermers RA, Khosla S, Atkinson EJ et al. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993-2001: an update on the changing epidemiology of the disease. J Bone Miner Res 2006;21:171-7.
2. Heath H 3rd, Hodgson SF, Kennedy MA. Primary hyperparathyroidism. Incidence, morbidity, and potential economic impact in a community. N Engl J Med 1980;302:189-93.
3. Vestergaard P, Mosekilde L. Incidence of primary hyperthyroidism, frequency of surgical intervention and mortality rates based on data from the National Patient Registry. Ugeskr Læger 2004;166:41-5.
4. Richert L, Trombetti A, Herrmann FR et al. Age and gender distribution of primary hyperparathyroidism and incidence of surgical treatment in a European country with a particularly high life expectancy. Swiss Med Wkly 2009;139:400-4.
5. Yu N, Donnan PT, Murphy MJ et al. Epidemiology of primary hyperparathyroidism in Tayside, Scotland, UK. Clin Endocrinol (Oxf) 2009;71:485-93.
6. Andersen TF, Madsen M, Jørgensen J et al. The Danish National Hospital Register. Dan Med Bull 1999;46:263-8.
7. Due P, Heitmann BL, Sørensen TI. The obesity epidemic in Denmark. Ugeskr Læger 2006;168:129-32.
8. Grey AB, Evans MC, Stapleton JP et al. Body weight and bone mineral density in postmenopausal women with primary hyperparathyroidism. Ann Intern Med 1994;121:745-9.
9. Bell NH, Epstein S, Greene A et al. Evidence for alteration of the vitamin D-endocrine system in obese subjects. J Clin Invest 1985;76:370-3.

10. Snijder MB, van Dam RM, Visser M et al. Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. J Clin Endocrinol Metab 2005;90:4119-23.
11. Gallagher JC, Nordin BE. Treatment with oestrogens of primary hyperparathyroidism in post-menopausal women. Lancet 1972;1:503-7.
12. Gallagher JC, Wilkinson R. The effect of ethinyloestradiol on calcium and phosphorus metabolism of postmenopausal women with primary hyperparathyroidism. Clin Sci Mol Med 1973;45:785-802.
13. Selby PL, Peacock M. Ethinyl estradiol and norethindrone in the treatment of primary hyperparathyroidism in postmenopausal women. N Engl J Med 1986;314:1481-5.
14. Marcus R, Madvig P, Crim M et al. Conjugated estrogens in the treatment of postmenopausal women with hyperparathyroidism. Ann Intern Med 1984;100:633-40.
15. Haldimann B, Trechsel U, Dambacher MA et al. Hyperparathyroidie primaire de la femme agee: effect des oestrogenes sur le metabolism calcique Schweiz Med Wochenschrift 1982;112:1242-5.
16. Grey AB, Stapleton JP, Evans MC et al. Effect of hormone replacement therapy on bone mineral density in postmenopausal women with mild primary hyperparathyroidism. A randomised controlled trial. Ann Intern Med 1996;125:360-8.
17. Diamond T, Ng AT, Levy S et al. Estrogen replacement may be an alternative to parathyroid surgery for the treatment of osteoporosis in elderly postmenopausal women presenting with primary hyperparathyroidism: a preliminary report. Osteoporos Int 1996;6:329-33.
18. Tisell LE, Carlsson S, Fjalling M et al. Hyperparathyroidism subsequent to neck irradiation. Risk factors. Cancer 1985;56:1529-33.
19. Schneider AB, Gierlowski TV, Shore-Freedman E et al. Dose-response relationships for radiation-induced hyperparathyroidism. J Clin Endocrinol Metab 1995;80:254-7.