FRAX*plus* adjustments for primary hyperparathyroidism

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* See appendix B

Introduction

The risk of fracture is increased in patients with primary hyperparathyroidism (PHPT) [1, 2, 3, 4, 5, 6, 7]. In regard to FRAX, a recent case control study showed that the risk of both hip fracture and other major osteoporotic fractures (MOF) was increased [7]. It is notable that hazard ratios were less than those reported in earlier studies [6], but consistent with a recent study [1], likely reflecting the increasing presentation of milder cases of primary hyperparathyroidism. Several studies have reported that the risk of death is increased in primary hyperparathyroidism [1, 7, 8, 9, 10, 11, 12], probably as a result of cardiovascular disease and cancer. The increased risk of death acts as a competing hazard for the calculation of fracture probability, but fracture probabilities were still higher in patients with primary hyperparathyroidism than in population-based controls [7].

The aim of this report is to document the manner in which traditional estimates of fracture probability can be adjusted in patients at diagnosis of primary hyperparathyroidism.

Methods

For the development of a PHPT adjustment for FRAXplus, the relationship between fracture and death hazards was examined in a large register-based survey of patients with primary hyperparathyroidism (n=6884) and matched controls (n=68665) in Denmark identified from hospital registers [7]. The incidence of death, hip fracture and major osteoporotic fracture without hip fracture (distal forearm, spine and humerus; other MOF -oMOF) were determined by censoring for PTX for computing fracture probabilities excluding the time after parathyroidectomy. To estimate the instantaneous hazard function for death and fracture risk, an extension of Poisson regression model was used [13, 14]. This studied the relationship between the risk of death or fracture on one hand and current time since index date (date of first diagnosis of PHPT), current age, current calendar year, sex, and diagnosis on the other hand. Details of the methodology are published elsewhere [7] and the model is given in table 1. Probabilities for fracture were calculated from the hazard functions of death, hip fracture and MOF in 1-year intervals of age from the age of 40 years in men and women for the calendar year 2005 [7]. Ten-year probabilities of hip fracture and MOF were similarly determined in controls. The ratio (Cases/controls) was adjusted to the general population assuming a prevalence of primary hyperparathyroidism of 1% [15].

Table 1. Hazard ratio (HR) and 95% confidence intervals of Poisson regression model for hip fracture, other major osteoporotic fractures (oMOF) and death.

	Hip fracture	oMOF	Death
Current time since index (HR per year)	**0.93 (0.92, 0.94)**	**0.93 (0.92, 0.94)**	1.00 (1.00, 1.00)
Current age $\leq$55 (HR per year)	**1.20 (1.09, 1.33)**	**1.08 (1.06, 1.10)**	**1.10 (1.08, 1.13)**
Current age 55-75 (HR per year)	**1.13 (1.11, 1.14)**	**1.04 (1.04, 1.05)**	**1.10 (1.10, 1.11)**
Current age $\geq$75 (HR per year)	**1.11 (1.11, 1.12)**	**1.03 (1.03, 1.04)**	**1.12 (1.12, 1.12)**

Current calendar year -2005 (HR per year)	**0.96 (0.94, 0.98)**	0.99 (0.98, 1.01)	0.99 (0.98, 1.00)
Current calendar year 2005+ (HR per year)	**1.02 (1.01, 1.03)**	**1.04 (1.03, 1.05)**	**0.97 (0.97, 0.98)**
Sex (0-F, 1-M)	**0.70 (0.63, 0.79)**	**0.40 (0.36, 0.44)**	**1.48 (1.43, 1.53)**
PHPT	**1.48 (1.29, 1.69)**	**1.26 (1.11, 1.42)**	**1.52 (1.44, 1.60)**

PHPT: primary hyperparathyroidism; F: female; M: male

Table 2 shows examples of the fracture probabilities in patients with primary hyperparathyroidism and controls, and the ratio which forms the basis of the FRAXplus adjustment at specific ages in men and women. Note that these adjustments are made in the absence of BMD. There are insufficient data for providing adjustments with input of BMD. All numerical data are provided in appendix A and graphically in Figure 1.

Table 2 FRAXplus adjustments for 10-year probability of hip fracture and major osteoporotic fracture at the time of first diagnosis. Numbers shown under cases and controls are 10-year probabilities of the relevant outcomes. The ratio is the adjustment to be applied in the presence of primary hyperparathyroidism.

Age (years)	Major osteoporotic fracture			Hip fracture		
	Cases	Controls	Ratio	Cases	Controls	Ratio
Men						
40	1.16	0.92	1.26	0.09	0.06	1.46
50	2.66	2.10	1.26	0.46	0.32	1.45
60	4.78	3.78	1.26	1.51	1.06	1.41
70	8.10	6.63	1.22	4.02	3.02	1.33
80	10.56	9.62	1.10	7.07	6.11	1.16
90	9.96	10.20	0.98	7.95	7.91	1.00
Women						
40	2.82	2.25	1.25	0.12	0.08	1.46
50	6.18	4.92	1.25	0.66	0.45	1.45
60	10.45	8.37	1.25	2.21	1.54	1.43
70	16.66	13.70	1.21	6.18	4.53	1.36
80	21.61	19.32	1.12	12.09	9.96	1.21
90	20.94	21.18	0.99	15.05	14.60	1.03

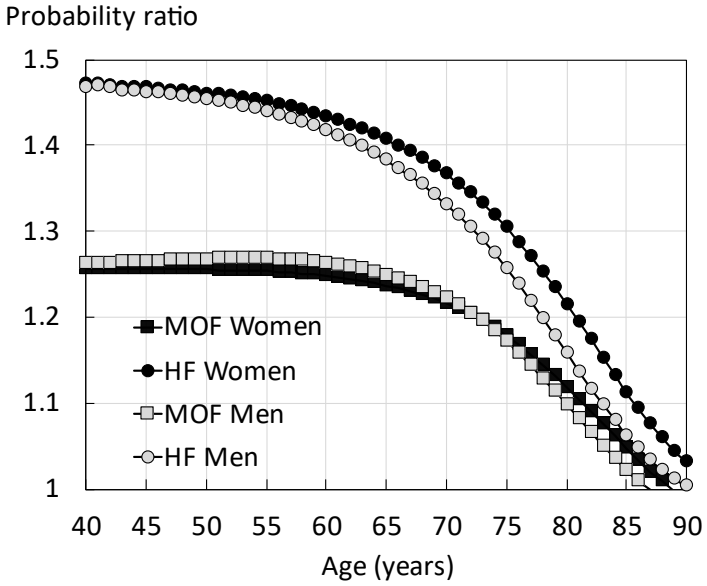

Figure 1. FRAXplus adjustment for 10-year probability of hip fracture (HF) and major osteoporotic fracture (MOF) at the time of first diagnosis.

It should be noted that these adjustments to FRAX are derived in the absence of bone mineral density (BMD). Thus, FRAXplus assumes that the same adjustments to fracture probabilities pertain when BMD is entered into FRAX.

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Appendix A. Ratios to adjust fracture probabilities in primary hyperparathyroidism by age and sex.

Age	Sex	Ratio for MOF probability	Ratio for HIP probability
40	female	1.25	1.46
40	male	1.26	1.46
41	female	1.25	1.46
41	male	1.26	1.46
42	female	1.25	1.46
42	male	1.26	1.46
43	female	1.25	1.46
43	male	1.26	1.46
44	female	1.25	1.46
44	male	1.26	1.46
45	female	1.25	1.46
45	male	1.26	1.46
46	female	1.25	1.46
46	male	1.26	1.45
47	female	1.25	1.46
47	male	1.26	1.45
48	female	1.25	1.46
48	male	1.26	1.45
49	female	1.25	1.45
49	male	1.26	1.45
50	female	1.25	1.45
50	male	1.26	1.45
51	female	1.25	1.45
51	male	1.26	1.44
52	female	1.25	1.45
52	male	1.26	1.44
53	female	1.25	1.45
53	male	1.26	1.44
54	female	1.25	1.45
54	male	1.26	1.44
55	female	1.25	1.44
55	male	1.26	1.43
56	female	1.25	1.44
56	male	1.26	1.43
57	female	1.25	1.44
57	male	1.26	1.43
58	female	1.25	1.43
58	male	1.26	1.42
59	female	1.25	1.43
59	male	1.26	1.42
60	female	1.25	1.43
60	male	1.26	1.41
61	female	1.24	1.42
61	male	1.26	1.41
62	female	1.24	1.42
62	male	1.26	1.40
63	female	1.24	1.41

63	male	1.25	1.39
64	female	1.24	1.41
64	male	1.25	1.39
65	female	1.23	1.40
65	male	1.25	1.38
66	female	1.23	1.39
66	male	1.24	1.37
67	female	1.23	1.39
67	male	1.24	1.36
68	female	1.22	1.38
68	male	1.23	1.35
69	female	1.22	1.37
69	male	1.23	1.34
70	female	1.21	1.36
70	male	1.22	1.33
71	female	1.21	1.35
71	male	1.21	1.31
72	female	1.20	1.34
72	male	1.20	1.30
73	female	1.19	1.33
73	male	1.19	1.29
74	female	1.19	1.31
74	male	1.18	1.27
75	female	1.18	1.30
75	male	1.17	1.25
76	female	1.17	1.28
76	male	1.16	1.23
77	female	1.16	1.27
77	male	1.14	1.22
78	female	1.14	1.25
78	male	1.13	1.20
79	female	1.13	1.23
79	male	1.11	1.18
80	female	1.12	1.21
80	male	1.10	1.16
81	female	1.10	1.19
81	male	1.08	1.14
82	female	1.09	1.17
82	male	1.06	1.12
83	female	1.07	1.15
83	male	1.05	1.10
84	female	1.06	1.13
84	male	1.04	1.08
85	female	1.05	1.11
85	male	1.02	1.06
86	female	1.03	1.09
86	male	1.01	1.05
87	female	1.02	1.07
87	male	1.00	1.03
88	female	1.01	1.06

88	male	0.99	1.02
89	female	1.00	1.04
89	male	0.98	1.01
90	female	0.99	1.03
90	male	0.98	1.00

Appendix B.

The Danish primary hyperparathyroidism study group

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