

Position Development Paper

Official Positions for FRAX[®] Clinical Regarding Smoking

From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX[®]

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on behalf of the FRAX[®] Position Development Conference Members^a*

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Abstract

The worldwide prevalence of smoking has been estimated at about 50% in men, and 10% in women, with larger variations among different populations studied. Smoking has been shown to affect many organ systems resulting in severe morbidity and increased mortality. In addition, smoking has been identified as a predictor of ten-year fracture risk in men and women, largely independent of an individual's bone mineral density. This finding has eventually lead to incorporation of this risk factor into FRAX[®], an algorithm that has been developed to calculate an individual's ten-year fracture risk. However, only little, or conflicting data is available on a possible association between smoking dose, duration, length of time after cessation, type of tobacco and fracture risk, limiting this risk factor's applicability in the context of FRAX[®].

Key Words: Smoking; FRAX[®]; fracture risk; dose-dependency; cessation; epidemiology.

Introduction

It has been estimated that in the year 2000 about 1.2 billion people have been smoking worldwide, and that about 5 million people have died from direct or indirect consequences of smoking (1,2). Of those who had died, about half were living in China, India, Latin America and other low- or middle-income countries outside Europe, and half were living in high-income countries and former socialist economies of Europe (3). Based on latest available trend analyses, it has been projected that by 2030 about 10 million smokers per year would die of a disease that has primarily been caused by smoking (3).

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Smoking prevalence has been shown to be significantly higher among men in low- and middle-income countries as compared to women (3) (Table). The difference between smoking prevalence among men and women appears to be smaller in high-income regions though. Worldwide, the prevalence of smoking has been estimated to be 47.5% in men, and 10.3% in women (4). Fortunately, while overall smoking prevalence continues to increase in many low- and middle-income countries, in many high-income countries decreases have been observed, primarily in men (1).

Smoking has been shown to affect a large number of organ systems resulting in various tobacco-related diseases, such as COPD, pneumonia and cancer, particularly lung cancer and cancers of the larynx and tongue (5,6). Furthermore, smoking has been linked to cardiovascular diseases, aortic aneurysm, peripheral vascular diseases and stroke, cancers of bladder, pancreas, esophagus, stomach, kidney, as well as leukemia, cataracts, periodontal disease, and fractures (7,8).

Smoking and its possible effect on fracture risk has first been mentioned in a study performed in postmenopausal

Table
Estimated Smoking Prevalence (by Gender) and Number of Smokers, 15 Years of Age and Over,
by World Bank Region, 2000

World Bank Region	Smoking prevalence			Total smokers	
	Males	Females	Overall	(millions)	(% of all smokers)
East Asia and Pacific	63%	5%	34%	429	38
Europe and Central Asia	56%	17%	35%	122	11
Latin America and Caribbean	40%	24%	32%	98	9
Middle East and North Africa	36%	5%	21%	37	3
South Asia	32%	6%	20%	178	15
Sub-Saharan Africa	29%	8%	18%	56	6
Low and middle income	49%	8%	29%	920	82
High income	37%	21%	29%	202	18

women almost 30 years ago (9). Since then, a considerable number of studies investigating a possible relationship between smoking and the risk of fractures have been performed, including several larger meta-analyses and reviews (8,10,11). An increase in fracture risk due to smoking has been demonstrated for women as well as for men, although, if taken together all osteoporotic fractures including hip fractures, the increase in risk appears to be higher in men than in women (10).

In a recently performed study, the relationship between smoking and different kinds of fractures have been investigated in a cohort of elderly men (12). After adjustment for a large number of different possible confounders including BMD, the hazard ratio (HR) for non-vertebral fractures, vertebral fractures, hip fractures, and for all fractures, was significantly higher as compared to controls.

A larger number of possible mechanisms have been suggested to be in causal relationship with increased fracture risk in smokers, such as a higher risk of falls, lower average body-mass indexes, direct toxic effects on bone, reduced calcium absorption, elevated cortisol levels, faster bone loss in postmenopausal women, or lower estrogen levels in those women who receive hormone replacement therapy (8). Some of these possible confounders, but not all of them, have been shown to be associated with decreased bone mineral density (BMD). In general, low BMD appears to account for only a minority of the increased fracture risk in smokers, albeit its association with increased fracture risk seems to increase with increasing age (8,10,13). Overall, data indicate that the risk of fractures is greater for smokers than it is for individuals of the same age, sex and BMD who do not smoke. Also, and most importantly, a meta-analysis involving ten large cohorts (EVOS/EPOS, DOES, CaMos, Rochester, Sheffield, Rotterdam, Kuopio, Hiroshima and two cohorts from Gothenburg) has demonstrated that the effect of smoking on fracture risk is over and above the one which could be explained by variations in BMD (10). Thus, together with a number of other risk factors that have been shown to be largely independent of BMD, current smoking has been

incorporated into a model for assessment of fracture probability in men and women (FRAX[®]) (14).

Methodology & Data Sources

To determine the effect of smoking on fracture risk, a Medline search limited to English language publications was performed. Items searched were: smoking and fracture, smoking and osteoporosis. Abstracts were reviewed and complete articles that correlated smoking to fractures were further evaluated.

Statements

Question: Is there sufficient evidence from recent studies to estimate how dose, type, duration and time from exposure for tobacco would impact on fracture probability as estimated by FRAX?

Official Position: While there is evidence that duration and dose of tobacco smoking may impact on fracture risk, quantification of this risk is not possible.

Grade: Fair, B, W

Rationale

Effect of Numbers of Cigarettes and Years Smoked

In a population-based case-control study in women involving 381 cases and 1,138 controls, smoking exposure and its effect on hip fracture risk was first investigated in relation to the number of pack-years consumed (the average number of cigarettes smoked per day times the number of years smoked divided by 20 cigarettes per pack) (15). Pack-years were categorized into four levels: 0,1–29,30–59, and > 60. The adjusted OR for the different levels was 0.94 (0.65–1.37; 95% CI), 1.11 (0.71–1.73; 95% CI), and 1.19 (0.57–2.47; 95% CI) indicative of a clear, albeit weak, dose-response relationship.

In another case-control study including a smaller number of men and women ≥ 65 years of age, the relationship between smoking and hip fracture risk was assessed according to the number of cigarettes smoked currently, at the age of 50, and at the age of 20 years (16). The amount of cigarettes

smoked per day were divided into 1–19/d, and ≥ 20 /d, respectively. The adjusted OR was 1.3 (0.5–3.4) and 1.6 (0.5–5.4) for the age of 20 years, 1.2 (0.6–2.5) and 2.3 (1.0–5.2) for the age of 50 years, and 1.4 (0.5–5.3), and 1.7 (0.7–4.3) for current smoking.

A case-control study performed in a small number of black women ($n = 144$; controls $n = 218$) aged ≥ 80 who had been admitted to a hospital with a first hip fracture, also assessed the association between the number of cigarettes smoked per day and hip fracture risk (17). In those who had been smoking less than 1 pack/per day the OR was 1.1 (0.5–2.4), and in those who had consumed at least 1 pack per day the OR was 2.0 (0.7–6.0).

In a large meta-analysis including nineteen cohort- and case-control studies, a possible association between fracture risk and smoking dose was investigated (8). In current female smokers as compared to non-smokers, the risk of hip fracture has been shown to be 17% greater at age 60, 41% greater at 70, 71% greater at 80, and 108% greater at age 90. The cumulative risk of hip fracture to age 85 in women has been estimated to be 19% in smokers and 12% in non-smokers, and to age 90 to be 37% and 22%, respectively. Furthermore it has been estimated that among all women, one hip fracture in eight is attributable to smoking (8).

In another large meta-analysis including ten prospective cohorts comprising European, Canadian, Australian and Japanese populations, the fracture risk of male smokers appeared to be slightly higher than the fracture risk in female smokers, and the authors suggested that this might be due to the fact that in general men smoke more than women, indicating a possible dose-risk relationship. However, a quantification of fracture risk in association with smoking dose could not be examined due to considerable differences in the way that smoking histories had been obtained (10).

Effect of Cessation of Smoking and Time Since Cessation

So far, only a few studies have been published addressing the issue of a possible effect of cessation of, and time after cessation of smoking on fracture risk. In a larger population-based case control study, the ORs for trochanteric fractures in former smokers who had stopped smoking ≥ 10 years ago was 1.15 (0.82–1.62) vs 2.37 (1.29–4.35) in those who had stopped within the past 10 years (18). In addition, the ORs for cervical fractures have been shown to be 0.94 (0.71–1.24) in those who quit smoking > 10 years ago, vs 1.37 (0.79–2.39) in those who quit smoking only within the past 10 years. In a Swedish case control study on postmenopausal women aged 50–81 years, smoking history was obtained in 1328 cases and 3312 controls (19). Among former smokers, the OR of hip fracture decreased with time after cessation. The reduction in age-adjusted ORs among former smokers was 2% per 5 years after cessation (OR, 0.98; 95% CI, 0.88–1.09). In comparison with current smokers, women who had stopped smoking within the past 14 years had a modest, nonsignificant decrement in risk (age-adjusted OR, 0.88; 95% CI, 0.66–1.17). In those who had quit smoking > 14

years ago, the risk declined to levels similar to those of never smokers. In a large meta-analysis the issue of a possible effect of cessation of smoking in the risk of osteoporotic fractures was addressed (11). The study indicated that cessation of smoking might be associated with a decrease in risk of hip fractures to normal or at least to a lower level as compared to the risk in current smokers. Furthermore, there seemed to be a linear downward trend in fracture risk with time since smoking cessation. It is noteworthy to mention that this association could not be demonstrated for smokers in Asia, and that in general an effect of smoking on fracture risk in Asian populations had not been detectable (20). In contrast, a case-control study performed in a smaller number of men was unable to find a significant difference in fracture risk between current smokers and former smokers (21).

In Summary

There is good evidence for smoking being an important risk factor for hip fractures and other osteoporotic fractures. The increased risk of fracture due to smoking, however, is largely independent of BMD. There is some evidence for a dose-response relation between the number of cigarettes smoked and the risk of hip fracture. Current smokers with the highest numbers of cigarettes smoked, and those with the highest number of pack-years, also have the highest risk of fractures. The risk of hip fractures in ex-smokers appears to be higher than in never-smokers, but lower as compared to current smokers. In general, the fracture risk appears to decrease with time since smoking cessation. However, a quantification of the risk of fractures as a function of dose is currently not possible.

Additional Questions for Future Research:

- a) Does the strength of the association between smoking and increased fracture risk vary among different (non-Asian) countries?
- b) Does the strength of the association between smoking and increased fracture risk vary among different ethnicities within countries?
- c) What is the reason (are the reasons) for the missing association between smoking and increased fracture risk in Asian regions?
- d) Does latitude in general have an impact on the effect of smoking on fracture risk?
- e) Does a “threshold dose” of smoking (i.e. a defined number of cigarettes smoked per day) exist, beyond which an individual’s fracture risk would be increased?
- f) Is there a dose of smoking beyond which a further increase in fracture risk would not be observed?
- g) Do female vs. male smokers have comparable fracture risk under comparable conditions?
- h) Do the different ingredients of tobacco (such as menthol), i.e. the type of tobacco, have different effects on fracture risk?

- i) Could differences in nutrition, life-style factors and other possible confounders in smokers vs non-smokers contribute to differences in fracture risk?
- j) What is the minimum of time after cessation of smoking at which fracture risk would have decreased to the risk of never-smokers, and are there differences among different populations and ethnicities?

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