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Bone mass density, fracture history, self-reported osteoporosis as proxy variables for estrogen and the risk of non-small-cell lung cancer—A population based cohort study, the HUNT study: Are proxy variables friends or faults?

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ABSTRACT

Lung cancer has the highest mortality of all cancers. Patients with early stage disease have the best cure rates and that emphasizes the importance of early detection. About half of all non-small cell lung cancers (NSCLC) are estrogen receptor positive. The impact of estrogen and its receptors for NSCLC carcinogenesis has been studied but is still unclear. Low estrogen levels are associated with osteoporosis. We hypothesize that low bone mineral density (BMD), a positive history of fracture or self-reported osteoporosis, used as a proxy variable for life time estrogen exposure, are associated with a low incidence of NSCLC. We analyzed data from a cohort study, the Nord-Trøndelag Health Study 2 (1995–1997) linked to the Norwegian Cancer Registry. Using the logistic regression model we calculated the odds ratio (OR) with a 95% confidence interval (CI) for the risk of NSCLC for the three proxy variables, stratified by sex. Participants older than 50 years of age, having measured bone density ($N = 18,156$), having answered the questions on self-reported fracture ($N = 37,883$) and osteoporosis ($N = 25,701$) and known body mass index (BMI) ($N = 29,291$), were evaluated for inclusion. In 6996 participants all these information was available in addition to tobacco use, and in women also hormonal replacement therapy (HRT). Lung function (FEV1 percent of predicted) was included in a sensitivity analysis. We identified 132 (1.9%) cases of NSCLC, 59 (1.2%) and 73 (3.3%) cases in women and men, respectively. Low BMD was associated with a higher risk of NSCLC, OR: 2.38, 95% CI: 1.09–5.18 and OR: 2.67, 95% CI: 1.39–5.16 in women and men, respectively. No association was found between the two other proxy variables and the risk of NSCLC. Inclusion of lung function in the model did not change the results. Contrary to our hypothesis, women and men with low BMD had a higher risk for NSCLC. In addition the study demonstrates that the risk depends on which proxy variable was chosen, and we may ask: are proxy variables reliable?

1. Introduction

Lung cancer has the second highest incidence rate and the highest mortality rate of all cancers [1]. Early detection followed by surgery provides the best survival rates. This emphasizes the importance of identifying new risk factors, in addition to known factors like age and tobacco smoking [2] that can be included in future screening programs.

About half of all non-small cell lung cancers (NSCLC) are estrogen receptor positive [3,4]. The impact of estrogen and its receptors for NSCLC carcinogenesis has been studied, and contradictory results are published [5–9]. Low estrogen levels are associated with osteoporosis [10–12]. Former studies have indicated that bone mineral density (BMD) in women as well as in men, might reflect life time estrogen exposure [13,14]. BMD should therefore reflect total estrogen exposure better than measured estrogen levels at one or few previous occasions [11,13–18]. In women estrogen therapy prevents bone loss after menopause. The prevalence of osteoporosis increases in both sexes [19]. Accordingly BMD, self-reported

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osteoporosis and self-reported previous fractures might be used as surrogate measures of life time estrogen exposure. BMD has been studied as a possible risk factor for cancer prostate, breast and colon cancer [20–26]. Low BMD is an important risk factor for fracture [27–30]. A positive fracture history was not associated with the risk of ovarian cancer but was associated with a decreased breast and endometrial cancer risk [31,32].

Self-reported osteoporosis has good reproducibility, high specificity, but low sensitivity compared to BMD based osteoporosis diagnosis [33].

Based on the current knowledge we anticipated that a lower cumulative estrogen exposure is associated with a lower risk of NSCLC in both sexes, and hypothesized that corresponding association could be found for surrogate measures of low estrogen exposure as low BMD, self-reported fracture history or self-reported osteoporosis, This hypothesis was studied in the second survey of a large population based cohort study in Norway, the Nord-Trøndelag Health Study (HUNT2).

2. Methods

2.1. Cohort

The HUNT study is a large population-based prospective cohort study in Nord-Trøndelag, Norway, having collected data in three surveys [34]. The county had about 127 000 inhabitants in 1996. In total 65 237 people, age 20 or above, participated in HUNT2 (69% of invited). This population is thoroughly studied and is fairly representative for the whole population in Norway. However, the county, in the middle of Norway, has few larger cities, has a slightly lower educational and income level, and the proportion of smokers is slightly below the Norwegian mean. In the present study we used data from HUNT2 (1995–1997) which were linked to lung cancer data from the Cancer Registry of Norway and the Death Cause Registry of Norway at Statistics Norway [35].

The observation period was from the day of inclusion in the HUNT2 survey until the event of lung cancer, death or the end of the study at December 31st 2008, whichever occurred first.

2.2. Outcome variable

2.2.1. Lung cancer

Lung cancer diagnosis was based on the classification system established by the World Health Organization (WHO) and was histologically verified (biopsy or cytology specimen) [36]. Estrogen receptors have only been found in NSCLC, therefore persons with small-cell lung cancer (SCLC) were excluded from the analyses. Norwegian law dictates that all new cases of cancer must be registered in the Cancer Registry of Norway.

2.3. Exposure variables

2.3.1. Bone mineral density

BMD was measured, in the period from August 1995 to June 1997, in the non-dominant distal forearm using single energy X-ray absorptiometry (SXA) (Osteometer DTX 100, Osteometer AS, Copenhagen). Measure site was 24 mm proximal from the point where the distance between radius and ulna was 8 mm.

BMD was measured as part of two HUNT2 sub studies: the Osteoporosis Study, inviting random samples of women born in the periods 1911–1930, 1936–1945 and 1954–1963, and the Lung Study, inviting a random sample of all participants, and those with self-reported "ever had asthma, use of asthma medication or asthma related symptoms during the last year" [37,38]. Sex specific BMD *z*-scores were calculated as (observed BMD minus mean BMD) divided by standard deviation (SD). Mean BMD and SD were calculated at three years intervals. However two years intervals were used during the ages of 48–62 years, due to increased bone loss within this group. BMD *z*-score were reported in tertiles defining low, medium and high *z*-scores.

2.3.2. Self-reported fracture history

The participants were asked about former fractures in the wrist, hip or vertebra. A total of 55 052 (84%) persons answered this question. An affirmative answer to at least one of these questions was defined as a positive self-reported fracture history. To avoid inclusion of high energy fractures, persons with fracture at the age 50 years or younger were excluded.

2.3.3. Self-reported osteoporosis

Self-reported osteoporosis was defined by an affirmative answer to one of these questions "Has your doctor ever said that you have osteoporosis" or "Do you have or have you had osteoporosis". A total of 52 804 (81%) answered this question.

2.4. Covariates

Potential confounders were evaluated by use of a Directed Acyclic Graph (not shown) and included in logistic regression analyses if they met the criteria for being defined as a confounder. These were tobacco smoking (four categories: 0, 1–20, 21–40 and >40 pack years), BMI (four categories according to the WHO criteria; <18.5 kg/m^2 = underweight, 18.5–24.9 kg/m^2 = normal weight, 25–29.9 kg/m^2 = overweight, ≥30 kg/m^2 = obesity). In women hormone replacement therapy (HRT) use, defined as ever/never users, was also included in the model. Persons invited to the lung study also performed spirometry. In a sensitivity analysis, lung function defined by prebronchodilator forced expiratory volume in one second/forced vital capacity ratio (FEV1/FVC ratio) (≤0.7/>0.7), was included as confounder, data were eligible for 4246 cases (45%). In analyses including BMD we did not adjust for age since BMD *z*-score was already adjusted for age. In analyses including self-reported fracture history or self-reported osteoporosis, the age at inclusion in the HUNT2 was included as a continuous variable in the model.

"Lung symptoms", included in a sub-analysis, was defined by a positive answer to questions on asthma related symptoms.

Only participants older than 50 years, having measured bone mineral density, having answered the questions on self-reported fracture and osteoporosis, with known body mass index (BMI) and tobacco use and in women with known HRT status were included in our study (Fig. 1).

2.5. Statistical analysis

All statistical analyses were stratified by sex. Logistic regression was used to assess odds ratio (OR) with 95% confidence interval for developing NSCLC. Two-sided tests were used and statistical significance was defined as $P < 0.05$. Lung function and self-reported lung symptoms were included in the model as sensitivity analyses.

The Hazard function was calculated by Cox regression models using NSCLC as the defined event, and BMD *z*-score, self-reported fracture history and self-reported osteoporosis as explorative variables, respectively. Included confounders were tobacco use, age at inclusion (not when using BMD *z*-score as the explorative variable), BMI, and in women HRT as well.

Interaction terms between all confounders, used in the model, and the exposure variables were tested, as a product in the logistic regression model.

To test the correlation between the explorative variables (BMD z-score, self-reported fracture and self-reported osteoporosis) the Chi-square test was used.