Progetto Menopausa Italia Study Group (including Graziottin A.)
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Menopausal status, hormone replacement therapy use and risk of self-reported physician-diagnosed osteoarthritis in women attending menopause clinics in Italy

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Abstract

Objective: In order to offer data on the association between menopausal status, hormone replacement therapy use and risk of self-reported physician-diagnosed osteoarthritis (OA) in women around menopause, we analyzed information collected in the framework of a large epidemiological study conducted in Italy.

Methods: Since 1997, a large cross sectional study has been conducting on the characteristics of women around menopause attending a network of first level outpatients menopause clinics in Italy for general counseling about menopause or treatment of menopausal symptoms. Eligible for the study were women consecutively observed at the participating centers. Up to March 2000, a total of 42.464 women (mean age 53 years) were observed. Women were asked, using the same questionnaire, about their general characteristics and habits, and if they suffer of OA diagnosed by a physician requiring medical or surgical treatment.

Results: A total of 12.521 women reported OA. The risk of OA increased with body mass index (BMI), the odds ratio, OR, being for BMI > or equal to 27 versus <24, 1.56 (95% CI 1.47-1.64). The risk increased with a history of osteoporosis/osteopenia (OR 1.65, 95% CI 1.57-1.74) and was lower in more educated women (OR high school/university degree vs. primary school degree 0.79, 95% CI 0.75-0.84). Considering menopausal status, women in spontaneous or surgical menopause were at increased risk of OA (OR 1.13, 95% CI 1.07-1.21, and 1.18, 95% CI 1.08-1.28, respectively, in women in surgical and spontaneous menopause). No clear relationship, however, emerged with age at menopause. Ever hormonal replacement therapy users were at decreased risk of OA, the OR being for ever users in comparison with never 0.73 (95% CI 0.69-0.78).

Conclusion: This analysis gives some epidemiological support to the hypothesis that estrogen deficiency may increased the risk of OA.

Introduction

The epidemiological observation that, after age 50, osteoarthritis (OA), particularly of the knee, is more common in females has suggested that estrogens deficiency may play a role in the onset or progression of the condition [1-3].

Some epidemiological cohort or case-control studies have shown a decreased risk of OA in estrogens replacement therapy users (ERT), however, other studies did not confirmed these findings [4-13]. Estrogens reduce the frequency of osteoporosis [14], which in turn is associated with the risk of OA [2,3], thus the protection given by estrogens on OA can be at least in part explained by their effect on osteoporosis.

Cause of early estrogens deprivation is also premature or early surgical or spontaneous menopause. Epidemiological data on the relationship between age at menopause and risk of OA are, however, extremely scanty [2,3].

In order to analyze the association between menstrual history, ERT use and risk of OA, we have analyzed data collected in a large epidemiological study conducted in Italy on women attending menopause clinics for counseling about or treatment of menopause [15-17].

Materials and methods

Between 1997 and 1999, a large cross sectional study was conducted on the characteristics of women around menopause attending a network of first level outpatients menopause clinics in Italy for general counseling about menopause or treatment of menopausal symptoms [15-17]. Eligible for the study were women who agreed to participate, consecutively, observed during the study period. The study protocol did not foresee any exclusion criteria.

The study started in 1997 in 25 centers. The number of centers increased to 268 in March 1999. Of those 63 were placed in North, 81 in the Center and 124 in the South of Italy.

Up to March 2000 a total of 42.464 women (mean age 53 years) were observed at the participating centers. All women, underwent a gynecological examination. Further, during the visit, they were asked, using a standard questionnaire, about their general characteristics and habits, reproductive and menstrual history, and a selected medical history. Clinical evidences and answers of the women were checked, when useful, with medical records. During the visit, the woman was also asked: "Do you suffer of OA diagnosed by a physician requiring medical or surgical treatment?" If woman answered yes, it was considered for the purpose of the present analysis as subject with OA. Thus the diagnosis of OA was selfreported. However, the gynecologist was asked to check whenever possible medical record to confirm self-reported diagnosis and in case of disagreement to verify with the woman the diagnosis. Laboratory and instrumental tests were requested on a clinical basis. In particular, the study protocol did not consider the measurement of bone mass density mandatory for all women.

Body mass index (BMI, kg m^{-2}) was categorized on the best possible approximation of tezile of BMI in the whole population. Postmenopausal women were defined as those with surgical menopause (i.e. bilateral oophorectomy with or without hysterectomy), women aged > 55 years who underwent hysterectomy without bilateral oophorectomy, plus those whose menstrual cycles had stopped more than 1 year before interview. Low bone density (i.e. osteopenia or osteoporosis) was defined according to WHO classification [18].

We computed odds ratios (ORs), as estimators of relative risk of OA. In order to account simultaneously for the effects of several potential confounding factors, we use unconditional multiple logistic regression, with maximum likelihood fitting, to obtain OR and their 95% confidence intervals [19]. The factors considered in the model are listed in the foot note of the table.

Results

Out of the 42.343 women for which information on self reported physician diagnosed OA was available (and which are considered in this analysis), 12.512 (29.6%) reported OA. Their distribution together with the distribution of the 29.822 cases who did not report OA is shown in **Table 1**.

The risk of OA increased with age, the OR being, in comparison with women aged <50 years, 1.22 (95% CI 1.14-1.30), 1.32 (95% CI 1.23-1.41) and 1.79 (95% CI 1.67-1.91) in women aged 50-52, 53-56 and >57, respectively.

Likewise the risk increased with BMI (OR for BMI > or equal to 27 vs. < 24, 1.56, 95% CI 1.47-1.64) with a history of osteoporosis/osteopenia (OR 1.65, 95% CI 1.57-1.74) and was lower in more educated (OR high school/university degree vs. primary school degree 0.79, 95% CI 0.75-0.84).

Considering menopausal status, women in spontaneous or surgical menopause were, after taking into account the effect of age, at increased risk of OA (OR 1.13, 95% CI 1.07-1.21, and 1.18, 95% CI 1.08-1.28, respectively, in women with surgical and spontaneous menopause). No clear relationship, however, emerged with age at menopause. Ever ERT users were at decreased risk of OA, the OR being for ever users in comparison with never 0.73, 95% CI 0.69-0.78.

Discussion

The main limitation of this analysis is the fact that diagnosis of OA was self-reported. Further we did not collected data on the localization of OA, and it is known that various factors may act differently on the risk of OA of the knee, the hip or the hand [2,3]. However, any misclassification of cases and control tends to reduce the epidemiological differences. In general, it has been shown a reasonable level of agreement between self reported or diagnosis by a physician [1]. Further, the prevalence of OA reported in our population is largely consistent with that reported in a large representative survey of health status of Italian women conducted by the National Institute of Statistics in a comparable calendar period [20].

Women considered in this analysis were women attending menopause clinics in Italy. This selective mechanism, however, should not affect the results of this analysis since we compared in the same data set women with and without OA, and it is unlikely that the presence of OA may selectively cause referring to the menopause clinics.

With these limitations, this analysis shows an association between osteopenia/osteoporosis, BMI and the risk of OA and gives some epidemiological support to the fact that, after taking into account the effect of age, post menopausal women are at increased risk of OA. ERT users were at decreased risk, thus suggesting that estrogens deficiency may be associated with OA. This association is not explained in this analysis by the potential confounding effect of osteoporosis/osteopenia which in turn is associated with estrogens deficiency too [14]. In fact, the estimated ORs of OA for postmenopausal women versus premenopausal ones and for ever HRT versus never users were, respectively, 1.17 and 0.73 when in the analysis terms for osteoporosis/osteopenia were included and 1.21 and 0.81 when they were not.

These results are in agreement with some, but not all, published papers on the issue. For example in a study conducted on more than 4.000 women, the OR of OA of the hip was 0.6 in users of HRT [5]. Similar suggestions emerged for the Framingham study [9]. Likewise a meta analysis of four studies indicated on OR of OA of the knee and of the hip of 0.8 in HRT users [6].

Conversely other studies did not confirm these results [13].

In biological terms, the presence of estrogens receptor in the synovium, that have been identified in animals and in humans [21-23] may explain a link between estrogens and OA.

With regard to the relationship between a history of osteopenia/osteoporosis and risk of OA published data show controversial results. Some authors have found a positive relation between bone mineral density (BMD) and the development of OA [24]. Recent data, however, tend to demonstrate an inverse relationship between BMD of the knee or the subchondral bone and the worsening of knee OA [25,26]. Our study shows an association between risk of OA and osteoporosis/osteopenia; however, the lack of information on the localization of OA does not offer the opportunity of analyzing the different effect of osteoporosis/osteopenia in specific localization such as knee.

In conclusion, this analysis gives some epidemiological support to the hypothesis that estrogens deficiency may increased the risk of OA.

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Table 1
Distribution of study subjects according to self reported physician-diagnosis of OA and selected factors

	Osteoarthrytis		OR
	Yes	No	(95% CI)
Age (years)			
< 50	2179 (17.4)	7350 (24.7)	1+
50-52	2627 (21.0)	7058 (23.7)	1.22 (1.14-1.30)
53-56	3186 (25.5)	7630 (25.6)	1.32 (1.23-1.41)
> 57	4529 (36.2)	7784 (26.1)	1.79 (1.67-1.91)
Education			
Primary school	5703 (45.5)	10524 (35.2)	1+
Middle school	2947 (23.5)	8316 (27.8)	0.76 (0.72-0.80)
High school/University	2816 (22.5)	7876 (26.4)	0.79 (0.75-0.84)
BMI (kg m^{-2})			
< 24	3341 (28.3)	9975 (36.4)	1+
24-26	3387 (28.7)	8177 (29.9)	1.20 (1.13-1.27)
≥ 27	5063 (42.9)	9219 (33.7)	1.56 (1.47-1.64)
Menopausal status			
Premenopause	1915 (15.3)	6156 (20.6)	1+
Surgical menopause	1417 (11.3)	3154 (10.6)	1.13 (1.07-1.21)
Spontaneous menopause	9210 (73.4)	20 573 (68.9)	1.18 (1.08-1.28)
Age at menopause			
Pre menopause	1915 (16.4)	6156 (22.7)	1+
< 50	4890 (41.8)	11194 (41.3)	1.23 (1.15-1.31)
50-52	3229 (27.6)	6682 (24.6)	1.21 (1.12-1.30)
≥ 53	1660 (14.2)	3097 (11.4)	1.20 (1.10-1.31)
Use of ERT			
No	10789 (86.0)	24542 (82.1)	1+
Yes	1753 (14.0)	5341 (17.9)	0.73 (0.69-0.78)
History of osteporosis/osteopenia			
No	9484 (75.6)	25318 (84.7)	1+
Yes	3058 (24.4)	4565 (15.3)	1.65 (1.57-1.74)

In some cases the sum does not add up the total due to missing values. OR, multivariate odds ratios including term for center plus the above listed variables. CI, confidence interval.