Increased Cancer Risk in Patients Referred to Hospital with Suspected Fibromyalgia

LENE DREYER, LENE MELLEMKJAER, SALLY KENDALL, BENTE JENSEN, BENTE DANNESKIOLD-SAMSØE, and HENNING BLIDDAL

ABSTRACT. ***Objective.*** To analyze whether fibromyalgia (FM) and FM-like symptoms are related to an increased incidence of cancer.

Methods. We identified 1361 patients referred on suspicion of FM in the period 1984-99 from hospital records. Following the American College of Rheumatology (ACR) criteria, patients were divided into subgroups with and without confirmed FM. The cohort was followed to the end of 1999 and linked to the files of the Danish Cancer Register. Site-specific standardized incidence ratios (SIR) were calculated.

Results. We found no association between FM and cancer in 1132 female patients with confirmed FM at our institution (SIR 1.2, 95% CI 0.8–1.8). In 106 women referred for muscle pain and/or tenderness who did not meet the criteria for FM, an increased overall SIR was observed (SIR 2.5, 95% CI 1.2–4.6), with increased risk for breast cancer (SIR 4.8, 95% CI 1.6–11.3) and lymphatic and hematological cancers (SIR 10.6, 95% CI 1.2–38.2). There were 4 lung cancers in 84 men with confirmed FM (SIR 12.6, 95% CI 3.4–32.4).

Conclusion. Neither confirmed FM nor those without confirmed FM predicted cancer. An increased risk of breast cancer was found among those who did not meet the ACR criteria for FM. These patients should be investigated if they develop any new or warning symptoms of malignancy, and treating physicians should be vigilant with screening procedures such as mammography. (J Rheumatol 2007;34:201–6)

Key Indexing Terms:
FIBROMYALGIA CANCER FOLLOWUP STANDARD INCIDENCE RATIO

Fibromyalgia (FM) is a condition of unknown etiology characterized by widespread pain and multiple tender points on examination[1]. The prevalence of FM in the general population is 1%–2% and is highest among women[2,3]. The symptoms of FM are not specific, while many differential diagnoses may be excluded by a thorough clinical examination and case history. There are several associations between pain conditions, muscle pain conditions, and malignant diseases. Generalized pain is a feature of many malignant diseases, including multiple myeloma and metastatic breast, lung, and prostatic cancers[4]. Two rheumatic conditions characterized by muscle pain and weakness, polymyositis and dermatomyositis, are associated with an increased risk of cancer, especially within a short time after the diagnosis of the rheumatic condition. They thus constitute a paraneoplastic syndrome[5]. There is evidence that patients with rheumatoid arthritis (RA), systemic sclerosis, primary Sjögren's disease, and systemic lupus erythematosus have an increased risk of cancer, particularly non-Hodgkin's lymphoma[6-11].

Few studies have investigated the risk of cancer among patients with FM, and the results are inconclusive. A study from the United States of self-reported comorbidity in patients with FM compared with RA and osteoarthritis patients found no significant difference regarding cancer diseases after adding anxiety as a covariate[12]. A British cohort study based on 2 population surveys reported increased incidence of female breast and prostate cancer, and borderline significantly increased risk of lung cancer and large bowel cancer among participants with self-reported generalized widespread pain, compared to people who reported no pain[13]. It is not known whether these results can be extrapolated fully or in part to patients with FM, as the participants were not clinically examined for FM.

In this incidence study we examined the overall and site-specific risk of cancer including the typical metastatic tumors and lymphatic and hematopoietic cancers in a cohort of patients with pain referred to a university hospital and examined for FM.

From The Parker Institute, Department of Rheumatology, Frederiksberg Hospital, Frederiksberg; Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen; and Multidisciplinary Pain Centre, H:S Rigshospitalet, Copenhagen, Denmark.

Supported by the OAK Foundation, The Danish Rheumatism Association, The Lily Benthine's Foundation, and The Neye Foundation.

L. Dreyer, MD, PhD; B. Jensen, MD, PhD; B. Danneskiold-Samsøe, MD, PhD, Professor, The Parker Institute, Department of Rheumatology, Frederiksberg Hospital; L. Mellemkjaer, MSc, PhD, Institute of Cancer Epidemiology; S. Kendall, MD, The Parker Institute, Multidisciplinary Pain Centre; H. Bliddal, MD, PhD, Professor, The Parker Institute, Department of Rheumatology, Frederiksberg Hospital.

Address reprint requests to Prof. H. Bliddal, Department of Rheumatology, The Parker Institute, Frederiksberg Hospital, DK-2000 Frederiksberg, Denmark. E-mail: hb@fh.hosp.dk

Accepted for publication August 23, 2006.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2007. All rights reserved.

Downloaded on March 13, 2024 from www.jrheum.org

MATERIALS AND METHODS

We used the database of the Department of Rheumatology, Frederiksberg Hospital, Copenhagen, to identify 1361 patients referred to the hospital under the diagnosis of FM in the period 1984-99. All patients referred for FM were registered in this database in the study period. Patients were referred from all parts of Denmark, but 63% lived in the Copenhagen area. During the study period all patients went through a medical examination by a clinician, and the 2 technicians or the clinician performed the tender point examination. The diagnosis was made primarily by the clinician, and the technicians did no diagnosing. Medical records of each patient were collected and reviewed blinded to the outcome, cancer, by one investigator (LD) to examine whether the patients fulfilled the American College of Rheumatology (ACR) 1990 criteria[1] for the classification of FM. In cases of uncertainty, the file was discussed with other investigators (HB or BDS). Briefly, the criteria require pain in all body quarters and axial pain for more than 3 months, and ≥ 11 of 18 predefined tender points at clinical examination. For patients examined before the introduction of the 1990 criteria with a tender point scheme used at that time, the tender point criterion was accepted as fulfilled in patients if they reported pain in 10 of 16 points at digital palpation and in patients recorded as having "universal muscle tenderness" by palpation according to the in-house examination. Data on pain history and tender points were sampled prospectively. Information on smoking habit and other medical diagnoses was obtained from the medical records. Hospital files in Denmark use the personal identification number ("CPR number"), unique to every Danish citizen, which incorporates sex and date of birth and permits accurate linkage of information between registers.

Statistical analysis. The cohort was linked to the Central Population Register for information on vital status and migration. Eight patients were excluded due to invalid CPR numbers, leaving 1353 patients in the analysis. The cohort was followed up for cancer incidence by linkage to the files of the Danish Cancer Register. The Danish Cancer Register is a population-based registry containing data on the incidence of cancer throughout Denmark since 1943. Reporting cancer was made mandatory by administrative order in 1987. The completeness and validity of the registry have been shown to be 95%–98% by linkage to independent data from the Hospital Discharge Registry, death certificates, and a pathology register[14]. Cancers are classified according to a modified Danish version of the International Classification of Disease-7[14,15]. The period of followup started at the date of the FM diagnosis, i.e., baseline, and ended at the date of emigration (n = 13), date of death (n = 48), or December 31 or 1999 (n = 1292), whichever occurred first. The expected number of cancers in the cohort was calculated by multiplying the number of person-years experienced by the cohort members by the cancer incidence rates in Danish men and women in 5-year age groups and calendar periods of observation. Standardized incidence ratios (SIR) of observed to expected numbers of cancer incidence and 95% confidence intervals (CI) were calculated, assuming a Poisson distribution of the observed cancers. The SIR were studied at short as well as longterm followup for each cancer site. In the analysis presented in Table 2 the first year of followup was excluded to reduce any potential surveillance bias due to extensive examination of these patients in the years preceding the visit at the hospital and the year after. To study the possible influence of changes in the use of diagnostic criteria on cancer, risk subanalyses were performed separately for patients diagnosed before and after the full implementation of the ACR criteria in the department (January 1, 1992).

RESULTS

Of the 1353 patients (1269 women, 84 men) referred to hospital for FM, 1189 (88%) fulfilled the criteria for FM (confirmed FM) and 131 (10%) did not fulfil the criteria (possible FM), while the medical records of 33 (2%) patients were lost. The main characteristics of the study cohort are given in Table 1. The cohort was followed for a total of 5298 years-at-risk for cancer (mean followup 3.9 yrs, range 0–16). A total of 55 cancers were observed among the 1353 patients, giving a significantly increased SIR of 1.40 (95% CI 1.1–1.8).

Among the 84 men referred to hospital for FM, a total of 5 cancers were observed (SIR 1.20, 95% CI 0.4–2.8): 4 lung cancer (SIR 6.26, 95% CI 1.4–13.5) and one non-Hodgkin's lymphoma (SIR 9.30, 95% CI 0.1–51.7). The 4 cases of lung cancers occurred among men with confirmed FM (SIR 12.6, 95% CI 3.4–32.4), and all were observed more than 1 year after examination for FM. The one case of non-Hodgkin's lymphoma was observed within the first year after examination in a patient whose medical records had been lost.

Table 2 gives the risk of overall cancer among female patients by years since baseline examination for FM at the hospital. An overall significantly increased cancer risk was observed in all patients combined during 0-16 years of observation, and a borderline significantly increased risk was observed in patients with possible FM and lost medical records. For patients with confirmed FM, the overall risk of cancer was not significantly elevated in any followup interval. During followup after more than 5 years, their risk was slightly below unity. There was no case of cancer within 1 year of the FM examination, but an excess of cancers was seen both 1–4 years and after more than 5 years of followup in patients with possible FM and patients with lost records. The overall cancer risk in all women referred to the hospital under the suspected diagnosis of FM was SIR 1.4 (95% CI 0.9–2.2) for patients diagnosed before January 1, 1992, and SIR 1.4 (95% CI 0.9–2.1) for patients diagnosed after that date. The corresponding data for patients with confirmed FM according to the ACR criteria were SIR 1.0 (95% CI 0.5–1.8) and SIR 1.3 (95% CI 0.8–2.0), respectively. An additional analysis revealed that among patients with confirmed FM, the average number of tender points was not higher in patients with cancer compared to patients without cancer, 17.6 versus 17.3 (p = 0.11). Similarly, among patients with possible FM no difference was observed in patients who developed cancer compared to others in the proportion of patients with 11 or more tender points but not fulfilling the ACR criteria, 2 of 10 versus 39 of 87, respectively (p = 0.18); data were missing in 9 cases.

Table 3 gives the cause-specific risk of cancer in all female patients, patients with confirmed FM, and patients with possible FM during 1–16 years of followup. There was a significantly increased risk of laryngeal cancer among female patients with confirmed FM on the basis of 2 cases. An increased SIR of female breast cancer was observed in possible FM cases, but no significant increased risk was observed in confirmed FM. The staging of breast cancer at the time of cancer diagnosis was investigated in the Danish Cancer Registry. Staging was the same in confirmed FM, in possible FM, and in patients with lost records. About 60%

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2007. All rights reserved.

Downloaded on March 13, 2024 from www.jrheum.org

Table 1. Descriptive characteristics of 1353 patients referred to hospital for fibromyalgia (FM) during 1984-99.

Characteristics	Women			Men		
	Confirmed FM, No. (%)*	Possible FM, No. (%)	Lost Medical File, No. (%)	Confirmed FM, No. (%)	Possible FM, No. (%)	Lost Medical File, No. (%)
Total	1132	106	31	57	25	2
Age at diagnosis, yrs						
19–29	37 (3)	8 (8)	2 (6)	3 (5)	3 (12)	0 (0)
30–49	689 (61)	49 (46)	11 (36)	28 (49)	9 (36)	1 (50)
50–69	396 (35)	46 (43)	15 (48)	24 (42)	9 (36)	1 (50)
70+	10 (1)	3 (3)	3 (10)	2 (4)	4 (16)	0 (0)
Year of diagnosis						
1984–87	30 (3)	11 (11)	5 (16)	7 (12)	5 (20)	0 (0)
1988–91	93 (8)	29 (27)	20 (65)	12 (21)	8 (32)	1 (50)
1992–94	232 (20)	17 (16)	5 (16)	11 (19)	2 (8)	0 (0)
1995–99	777 (69)	49 (46)	1 (3)	27 (48)	10 (40)	1 (50)
Fulfil anamnestic criteria**						
Yes	1132 (100)	28 (26)	— (—)	57 (100)	4 (16)	— (—)
No	0 (0)	78 (74)	— (—)	0 (0)	21 (84)	— (—)
Data missing	0 (—)	0 (—)	31 (—)	0 (—)	0 (—)	2 (—)
Fulfil objective criteria†						
Yes	1132 (100)	41 (43)	— (—)	57 (100)	4 (22)	— (—)
No	0 (0)	54 (57)	— (—)	0 (0)	14 (78)	— (—)
Data missing	0 (—)	11 (—)	31 (—)	0 (—)	7 (—)	2 (—)
Body mass index, kg/m^2						
< 20, underweight	29 (3)	4 (8)	— (—)	0 (00	0 (0)	— (—)
20–24.9, normal weight	469 (49)	32 (59)	— (—)	18 (45)	2 (50)	— (—)
25–29.9, moderate overweight	276 (29)	11 (20)	— (—)	17 (42)	0 (0)	— (—)
30, severe overweight	175 (19)	7 (13)	— (—)	5 (13)	2 (50)	— (—)
Data missing	183 (—)	52 (—)	31 (—)	17 (—)	21 (—)	2 (—)
Also diagnosed with						
Primary Sjögren's syndrome	1 (0.1)	2 (2)	— (—)	0 (0)	0 (0)	— (—)
Rheumatoid arthritis	4 (0.4)	1 (1)	— (—)	0 (0)	0 (0)	— (—)
Psoriatic arthritis	2 (0.2)	0 (0)	— (—)	0 (0)	0 (0)	— (—)
Polymyositis	1 (0.1)	0 (0)	— (—)	0 (0)	0 (0)	— (—)
Ankylosing spondylitis	0 (0)	0 (0)	— (—)	1 (2)	0 (0)	— (—)
Data missing	0 (—)	0 (—)	31 (—)	0 (0)	0 (0)	2 (—)
Smoking habit						
Non-smokers	345 (43)	23 (32)	— (—)	16 (41)	7 (44)	— (—)
Ex-smokers	22 (3)	3 (4)	— (—)	0 (0)	2 (12)	— (—)
Current smokers	425 (54)	45 (63)	— (—)	23 (59)	3 (19)	— (—)
Heavy smokers (15+ g/day)	245 (58)	28 (62)	— (—)	16 (70)	4 (25)	— (—)
Data missing	340 (—)	35 (—)	31 (—)	18 (—)	9 (—)	2 (—)

* Percentage of patients with available data. ** Pain in all body quarters and axial pain for more than 3 months. † Eleven or more of 18 predefined tender points at clinical examination.

Table 2. Observed (Obs) numbers and standardized incidence ratio (SIR) of overall cancer among female patients by time since examination for fibromyalgia (FM) at hospital.

Years Since Examination	All Patients, n = 1269		Patients with Confirmed FM, n = 1132		Patients with Possible FM, n = 106		Patients with Lost Medical Record, n = 31	
	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
0–16	50	1.4 (1.1–1.9)	34	1.2 (0.8–1.7)	10	2.2 (1.0–4.0)	6	2.8 (1.0–6.1)
< 1	7	1.0 (0.4–2.1)	7	1.2 (0.5–2.4)	0	—	0	—
1–4	29	1.6 (1.1–2.3)	20	1.4 (0.8–2.1)	6	2.9 (1.0–6.2)	3	3.0 (0.6–8.7)
> 5	14	1.4 (0.7–2.3)	7	0.9 (0.4–1.9)	4	2.1 (0.6–5.4)	3	3.4 (0.7–9.8)

Confidence interval excludes the value 1.0.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2007. All rights reserved.

Downloaded on March 13, 2024 from www.jrheum.org

Table 3. Observed (Obs) numbers and standardized incidence ratio (SIR) of cancer among female patients referred to hospital for a diagnosis of fibromyalgia (FM) followed 1–16 years after examination.

Cancer Site	All Patients*, n = 1269		Patients with Confirmed FM, n = 1132		Patients with Possible FM, n = 106	
	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
All	43	1.5 (1.1–2.1)	27	1.2 (0.8–1.8)	10	2.5 (1.2–4.6)
Buccal cavity and pharynx	1**	2.7 (0.0–15.2)	1	3.2 (0.0–19.1)	0	— (—)
Digestive organs	4	1.1 (0.3–2.7)	2	0.7 (0.1–2.5)	0	— (—)
Colon	4	2.5 (0.7–6.3)	2	1.6 (0.2–5.9)	0	— (—)
Larynx	2	18.5 (2.1–66.9)	2	23.2 (2.6–83.7)	0	— (—)
Lung	3	1.1 (0.2–3.3)	2	0.9 (0.1–3.4)	1	2.6 (0.0–14.4)
Breast	18	2.3 (1.4–3.7)	11	1.8 (0.9–3.1)	5	4.8 (1.6–11.3)
Reproductive organs	3	0.8 (0.2–2.5)	3	1.1 (0.2–3.1)	0	— (—)
Urinary organs	1	0.9 (0.0–5.1)	1	1.2 (0.0–6.7)	0	— (—)
Non-melanoma Skin cancer	5	1.1 (0.4–2.6)	2	0.6 (0.1–2.0)	2	3.2 (0.4–11.5)
Lymphatic and hematopoietic	5	3.9 (1.3–9.2)	3	3.0 (0.6–8.9)	2	10.6 (1.2–38.2)
Non-Hodgkin's lymphoma	3	5.2 (1.0–15.1)	2	4.4 (0.5–15.7)	1	12.0 (0.2–66.8)
Other specified sites	0	— (—)	0	— (—)	0	— (—)
Secondary and unspecified sites	1	1.5 (0.0–8.2)	0	— (—)	0	— (—)

Confidence interval excludes the value 1.0. * All patients with confirmed FM, possible FM and lost medical file. ** Salivary gland.

of the tumors were localized, and 40% had regional spreading. No patient had metastatic breast cancer at the time of diagnosis. Ten cases of female breast cancer were observed in all patients examined for FM before the age of 50 years (SIR 3.0, 95% CI 1.4–5.6). Among these young patients, a nonsignificant increased SIR of female breast cancer was observed in both confirmed and possible FM cases (SIR 2.1, 95% CI 0.8–4.7 and SIR 6.0, 95% CI 0.7–21.8, respectively). An excess incidence of lymphatic and hematological cancers was observed among patients with confirmed FM and patients with possible FM. Out of a total of 5 cases, 3 were non-Hodgkin's lymphoma. All 3 cases of non-Hodgkin's lymphoma occurred among female patients examined before the age of 50 years: 2 in patients with confirmed FM (SIR 11.3, 95% CI 1.3–40.8) and one patient with possible FM (SIR 47.9, 95% CI 0.6–266.6). At baseline, none of these patients who developed non-Hodgkin's lymphoma had a history of therapy with immunosuppressive agents. The female patients with lost medical records had an overall increased cancer risk (SIR 3.2, 95% CI 1.2–6.9) based on 6 cases. An excess of colon cancer (SIR 15.1, 95% CI 1.7–54.7) and breast cancer (SIR 4.2, 95% CI 0.5–15.2) was observed.

DISCUSSION

This was the first prospective study of cancer incidence among patients with FM, which included clinical examination at hospital, a blinded review of the diagnosis according to ACR criteria, data from a complete nationwide cancer registry, and up to 16 years of followup. Previous studies have been based on FM defined as self-reported, generalized widespread pain based on population surveys[13] or self-reported cancer diseases in patients with FM[12]. We report a small increase in the overall risk for cancer among female patients referred to hospital for evaluation for suspected FM. In general, confirmed FM or generalized pain did not predict cancer. Interestingly, an increased risk of breast cancer was found among those who did not meet the ACR criteria for FM. Other cancer types of interest among patients with FM may be lymphatic and hematological and cancer of the respiratory system. Treating clinicians should be aware that these patients should be investigated if they develop any new or warning symptoms of malignancy and should be vigilant with screening procedures such as mammography.

The quality of the FM diagnosis from the records must be regarded as high, as patients were examined according to international standards and the diagnosis was reviewed, blinded to cancer outcome, using the ACR 1990 criteria for FM[1]. The observer reliability of the involved clinicians with regard to clinical examination was not tested. There was, however, no referral bias to the individual clinicians, and the clinicians were not aware at that time of a later followup for cancer incidence. The quality of the Danish Cancer Registry is acknowledged to be very high[14].

The medical records of 33 patients were missing. It is therefore not possible to determine whether or not these patients had FM. Assuming that these patients were similar to the rest of the cohort in the clinical signs of FM, about 80% would have been classified as FM and 20% as possible FM. Assuming that all the patients with missing records, the possible FM, and the confirmed FM constituted a characteristic population of "FM-like disease," the estimates would have been indicative of a definite increase in overall cancer risk in this cohort with chronic pain. Some of the patients with possible FM may in fact have had "borderline FM" or early FM. Tenderness and symptoms in FM are suggested to be placed at one end of a continuum of pain and tenderness in the population, and thus in a broader sense there is no dis-

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2007. All rights reserved.

Downloaded on March 13, 2024 from www.jrheum.org

crete point at which FM does or does not exist[16]. It is difficult to determine whether the group of patients with possible FM is at one end of a continuum of FM patients or constitutes a separate group with no connection to FM. However, the marked higher cancer risk in this group emphasizes that care should be taken to thoroughly investigate the clinical background in patients with borderline symptoms of FM.

It may be argued that the increased cancer risk in the referral cohort was due to the selection of patients with other rheumatic diseases and FM symptoms into the cohort. This might have been a concern in relation to RA, systemic sclerosis, primary Sjögren's syndrome, and systemic lupus erythematosus, since all of these are known to be associated with cancers, especially non-Hodgkin's lymphoma. Our data do not suggest this is a problem, however, since none of the 11 patients with other rheumatic diseases developed a cancer disease during followup.

It may also be argued that the observed excess risk of cancer was due to selection of patients who had not been carefully examined for cancer diseases that can mimic FM symptoms, especially in the early calendar period of the study. Further, patients referred to hospital may be more prone to disease than patients with similar diagnoses in general practice. In some analyses the first year of followup data were excluded to reduce any potential surveillance bias due to extensive examination of these patients in the years preceding the visit at the hospital and the year after. Patients who consult their primary care physician due to pain all over the body will in most cases be subjected to a wide program of investigation, including blood tests, radiology, and referrals to various specialists. Such extensive investigation increases the probability of diagnosing a cancer at an early stage. A patient with newly diagnosed cancer is not likely to be referred under the diagnosis of FM to a hospital because of pain, even though they actually may suffer from FM. It is therefore likely that the cancer risk seen the first year of observation after the FM diagnosis is influenced by a false lower risk of cancer because FM patients with cancer did not enter the cohort. Pulling in the other direction is the possible selection into the cohort of cancer patients with symptoms that mimic FM. However, that selection bias is not probable, as the excess risk of cancer was observed only at middle and longterm followup of major importance, and because the risk of cancer was not higher in the early calendar period of the study compared to the late period. The late occurrence of cancers in our data may also be interpreted as an indication that patients with musculoskeletal pain may run into further risk factors because of the disease, e.g., changes in lifestyle or medication.

An increased risk of lung cancer was observed among men referred for FM. That the increased risk was observed only in male patients and not in female patients argues against a true association between FM and lung cancer, assuming that FM is the same disease in men and women. It is more likely that the observed association is caused by heavy smoking (the patients who developed lung cancer were all smokers) or occupational exposure to lung carcinogens in male FM patients compared to the general population. The increased risk of laryngeal cancer can be explained by the higher prevalence of smoking in FM patients compared to the general population of the Copenhagen area of 44%[17]. Our results for lung cancer are in agreement with observations in the UK study of patients with self-reported widespread pain, with increased risk of lung cancer only in male patients[13].

A significantly increased risk of female breast cancer was observed in patients referred for the diagnosis of FM. Metastatic breast cancer is known to cause generalized pain and may mimic FM symptoms. However, in our study none had metastatic cancer disease. Further, the increased risk was observed more than 1 year after the time of FM examination. Thus, pain caused by metastasis at the time of FM diagnosis does not seem to explain the findings. Risk factors for female breast cancer include genetic factors[18], age of menstruation and menopause, nulliparity, use of hormones in contraceptive and menopausal therapy[19], alcohol consumption[20], menopausal obesity[21], and probably low physical activity[20]. We cannot rule out that the prevalence of exposure to these factors may differ in patients referred to hospital with suspected FM compared to the general population. In addition, regional variations in incidence are observed in Denmark, and are probably due to differences in distribution of risk factors. The incidence of female breast cancer is higher in the capital, Copenhagen, where the age-standardized incidence is 130 per 100,000 woman-years compared to 100 in Denmark as a whole[22]. However, a population based study from the UK reported no association between chronic widespread pain and sex hormonal factors, i.e., oral contraceptive use, hormone replacement therapy use, or age at menopause[23]. A German study has reported that associations with low alcohol intake, late menarche, and rare pregnancies are specific for subjects with FM, factors that may affect the risk of breast cancer in different directions[24]. It is well documented that FM patients have low physical activity due to functional disability intolerance, and this may contribute to the excess observed risk of breast cancer[3,25]. In 1993 the prevalence of moderate and severe overweight in Danish women aged 30–60 years was 26% and 11%, respectively[26]. Thus the prevalence of overweight in our study was higher in the patients with confirmed FM compared to the general population, but at the same level in patients with possible FM. Therefore, overweight may explain some of the excess risk of breast cancer observed in older menopausal patients. However, overweight can only partly explain the excess risk of cancer in patients diagnosed with FM before the age of

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2007. All rights reserved.

Downloaded on March 13, 2024 from www.jrheum.org

50, and cannot explain the excess risk in the group of patients with possible FM.

Our data do not allow us to determine whether the observed increased risk of female breast cancer can be partly or completely explained by these possible confounding factors. The results differ from the observations in the UK study of patients with self-reported widespread pain with increased risk of female breast cancer, in which there was an incidence rate ratio of 3.67 (95% CI 1.39–9.68)[13]. Thus the risk in our data was not largest in patients with widespread pain, but on the contrary was greatest in patients who did not fulfil the ACR classification criteria.

The increased risk of lymphatic and hematopoietic cancers observed in the total referral group was mainly due to a significantly increased risk of non-Hodgkin's lymphoma — 3 cases. An increased risk of non-Hodgkin's lymphoma was observed in women with FM diagnosed before the age of 50 years. As noted above, none of the patients had a record at baseline of any other rheumatic disease or medically induced immunosuppression known to be associated with such types of cancer. In the UK population study of subjects with widespread pain, no separate risk estimate for lymphopoietic and hematopoietic cancers was reported[13]. Further studies are warranted to investigate whether patients with muscle pain and tenderness have an increased risk of lymphopoietic and hematopoietic cancers including non-Hodgkin's lymphoma.

In this first study of cancer incidence among patients referred to hospital with diagnosis of suspected FM, we found an increased risk of female breast cancer among unconfirmed cases who did not meet the ACR criteria for FM. Widespread pain in cases of confirmed FM did not predict cancer in general. Other cancer types of interest among FM patients may be lymphatic and hematological and of the respiratory system. The observation that an excess of neoplasia occurred after a lag-phase indicates a focus on carcinogenic risk factors and malignancies during longterm followup in patients with FM-like symptoms.

ACKNOWLEDGMENT

We thank the laboratory technicians Sala Hirschorn, Jette Nielsen, MSc, and Christian C. Holm; and Sofie Bliddal, Kasper Dreyer, and Emil Jørsboe for their skillful help.

REFERENCES

1. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.
2. Prescott E, Kjoller M, Jacobsen S, Bulow PM, Danneskiold-Samsoe B, Kamper-Jorgensen F. Fibromyalgia in the adult Danish population: I. A prevalence study. Scand J Rheumatol 1993;22:233-7.
3. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19-28.
4. Reilly PA. The differential diagnosis of generalized pain. Baillieres Best Pract Res Clin Rheumatol 1999;13:391-401.
5. Hill CL, Zhang Y, Sigurgeirsson B, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet 2001;357:96-100.
6. Leandro MJ, Isenberg DA. Rheumatic diseases and malignancy — is there an association? Scand J Rheumatol 2001;30:185-8.
7. Myllykangas-Luosujarvi R, Aho K, Isomaki H. Mortality from cancer in patients with rheumatoid arthritis. Scand J Rheumatol 1995;24:76-8.
8. Rosenthal AK, Mclaughlin JK, Gridley G, Nyren O. Incidence of cancer among patients with systemic sclerosis. Cancer 1995;76:910-4.
9. Jacobsen S, Halberg P, Ullman S. Mortality and causes of death of 344 Danish patients with systemic sclerosis (scleroderma). Br J Rheumatol 1998;37:750-5.
10. Kauppi M, Pukkala E, Isomaki H. Elevated incidence of hematologic malignancies in patients with Sjogren's syndrome compared with patients with rheumatoid arthritis (Finland). Cancer Causes Control 1997;8:201-4.
11. Mellemkjaer L, Andersen V, Linet MS, Gridley G, Hoover R, Olsen JH. Non-Hodgkin's lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus. Arthritis Rheum 1997;40:761-8.
12. Wolfe F, Hawley DJ. Evidence of disordered symptom appraisal in fibromyalgia: increased rates of reported comorbidity and comorbidity severity. Clin Exp Rheumatol 1999;17:297-303.
13. McBeth J, Silman AJ, Macfarlane GJ. Association of widespread body pain with an increased risk of cancer and reduced cancer survival: a prospective, population-based study. Arthritis Rheum 2003;48:1686-92.
14. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry — history, content, quality and use. Dan Med Bull 1997;44:535-9.
15. Danish National Board of Health. Cancer incidence in Denmark 1998. Copenhagen: Danish National Board of Health; 2002.
16. Wolfe F. The relation between tender points and fibromyalgia symptom variables: evidence that fibromyalgia is not a discrete disorder in the clinic. Ann Rheum Dis 1997;56:268-71.
17. Prescott E, Osler M, Andersen PK, et al. Has risk associated with smoking increased? Results from the Copenhagen Center for Prospective Population Studies. Int J Epidemiol 1997;26:1214-8.
18. Wooster R, Weber BL. Breast and ovarian cancer. N Engl J Med 2003;348:2339-47.
19. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. Lancet Oncol 2001;2:133-40.
20. Key TJ, Allen NE, Spencer EA, Travis RC. Nutrition and breast cancer. Breast 2003;12:412-6.
21. Barnett JB. The relationship between obesity and breast cancer risk and mortality. Nutr Rev 2003;61:73-6.
22. Oksbjerg S, Mellemkjoer L, Johansen C. Incidence and mortality of breast cancer among women in Denmark 1943-1992 [Danish]. Ugeskr Laeger 1997;159:7134-40.
23. Macfarlane TV, Blinkhorn A, Worthington HV, Davies RM, Macfarlane GJ. Sex hormonal factors and chronic widespread pain: a population study among women. Rheumatology Oxford 2002;41:454-7.
24. Schochat T, Beckmann C. Sociodemographic characteristics, risk factors and reproductive history in subjects with fibromyalgia — results of a population-based case-control study [German]. Z Rheumatol 2003;62:46-59.
25. Kop WJ, Lyden A, Berlin AA, et al. Ambulatory monitoring of physical activity and symptoms in fibromyalgia and chronic fatigue syndrome. Arthritis Rheum 2005;52:296-303.
26. Heitmann BL. Ten-year trends in overweight and obesity among Danish men and women aged 30-60 years. Int J Obes Relat Metab Disord 2000;24:1347-52.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2007. All rights reserved.

Downloaded on March 13, 2024 from www.jrheum.org