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Predictors of malignancy development in patients with chronic pruritus☆

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ABSTRACT

Background: Patients with pruritus have been shown to have an increased incidence of certain subtypes of malignancy.
Objective: To assess predictors of malignancy in patients with chronic pruritus without prior dermatologic diagnoses.
Methods: Case-control study of 398 patients with chronic pruritus who developed a malignancy were compared with 8346 patients with chronic pruritus who did not develop a malignancy. Primary outcomes were odds of developing incident malignancy.
Results: Age greater than 60 years (OR 4.04, 95% CI 3.08, 5.31), male sex (OR 1.39, 95% CI 1.13, 1.71) and liver disease (OR 2.37, 95% CI 1.00, 5.65) were predictors of malignancy development in patients with chronic pruritus and non-diseased skin. In an exploratory analysis with multiple imputation via chained equations, age greater than 60 years (OR 4.13, 95% CI 3.15, 5.42), male sex (OR 1.26, 95% CI 1.02, 1.55), and current or prior smoking (OR 2.02, 95% CI 1.42, 2.88) were predictors of malignancy development in patients with chronic pruritus and non-diseased skin.
Limitations: Potential for misclassification and detection biases. Missing data.
Conclusions and relevance: In patients with chronic pruritus without concomitant dermatologic diagnoses, older age, male sex, liver disease and tobacco abuse increase the odds of an underlying malignancy.
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1. Background

Chronic pruritus, defined as itch lasting for equal to or greater than six weeks, is caused by dermatologic, psychiatric and systemic illnesses [1]. Systemic illnesses well known to be associated with pruritus include chronic renal failure, liver disease, thyroid disease, HIV infection, and malignancies [1]. While it is well established that patients diagnosed with certain malignancies (namely lymphomas and leukemias) have high rates of associated pruritus, there is limited data framing pruritus as a predictor of malignancy [2–4]. Two recent studies have suggested that pruritus may be a sign of malignancy. Johannesdottir et al. calculated standardized incidence ratios of cancer for a nationwide sample of Danes with one or more codes for pruritus compared to Danes without codes for pruritus and found a statistically significant increase in cancer incidence in those patients with pruritus [4]. They reported an overall SIR of cancer of 1.13 (95% CI 1.07–1.20) [4]. When they stratified their results by sex, only men had a statistically significant increase of cancer SIR (1.22 95% CI 1.13–1.33) [4]. Interestingly and contrary to anecdotal beliefs, the SIR was higher in those patients with pruritus who had a previous diagnosis of dermatologic disease (SIR 1.20, 95% CI of 1.08–1.33) compared to those patients without a previous diagnosis of dermatological disease (SIR 1.10, 95% CI 1.02–1.18) [4]. Using a large population-based cohort study design, our group has shown that patients with chronic pruritus without prior dermatologic diagnoses ("group 2 patients" as defined by the

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International Forum on the Study of Itch [1]) are not at a statistically significant increased risk of malignancy overall, but do have a statistically significant risk of developing hematological and bile duct malignancies within 5 years of their chronic pruritus diagnosis [3]. Our study differed from Johannesdottir et al. in that we only included patients without prior dermatologic diagnoses and all of our patients had chronic pruritus (defined as itch lasting six weeks or longer). Within our previous study 398 patients with chronic pruritus and no prior dermatologic diagnoses developed a malignancy within 5 years of their chronic pruritus diagnosis. In this study we sought differences between the group of patients with normal skin and chronic pruritus who developed a cancer and those patients with normal skin and chronic pruritus who did not develop a cancer. Delineating patients with chronic pruritus and normal skin who are at highest risk of developing a malignancy will help us to narrow our use of screening tests for malignancy detection.

2. Methods

2.1. Study population

This study was carried out with The Health Improvement Network (THIN). THIN is an anonymized population-based electronic medical records database that contains reliable health information on approximately 11 million patients in the UK [5,6]. Longitudinal data on anonymized patients spans an average of 9 years [5,6]. THIN data is populated by General Practitioners during patient visits. THIN includes information on patient demographics, medical diagnoses (READ codes), laboratory results, and prescriptions. THIN data from 1995 to 2012 were used in this study. Methods conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [7]. This study was approved by the University of Pennsylvania Institutional Review Board and the THIN Scientific Review Committee.

Previously we generated a cohort of adult patients with chronic pruritus (defined as having two READ codes for pruritus separated by at least 6 weeks), who did not have dermatologic conditions associated with pruritus (examples include eczema, psoriasis and urticaria) nor malignancy (other than non-melanoma skin cancers) at the time of their enrollment [3]. This cohort of patients was followed until they developed a malignancy, died, or 5 years had passed. Within this original cohort, 398 patients with chronic pruritus without prior dermatologic diagnoses developed a malignancy and 8346 patients with chronic pruritus without prior dermatologic diagnoses did not develop a malignancy. This case-control study was performed to assess risk factors for malignancy in patients with chronic pruritus. Covariates associated with the development of pruritus (liver disease, renal disease, diabetes, thyroid disease, depression, anxiety, smoking, alcohol use, and body mass index) were included in the analysis.

2.2. Statistical analysis

Patient demographics and covariates were summarized and compared using Pearson χ^2 test for dichotomous variables with quantities greater than 5, and Fisher's exact test for dichotomous variables with quantities less than 5 and t tests for continuous variables. Logistic regression, using a forward selection process, was used to assess whether covariates were a predictor of incident cancer. Smoking status and alcohol use unfortunately had a large percentage of missing data and the missing data was not missing at random (i.e., patients with chronic itch who developed a malignancy had less missing data than patients with chronic itch who did not develop a malignancy). The decrease in missing data in those patients who developed a cancer is likely a reflection of an increase number of doctor visits and therefore more opportunities for the doctor to code these covariates. We highly suspected that smoking and alcohol use are in the causal pathway of malignancy development in these patients and therefore carried out an exploratory analysis of these covariates using imputed data generated with multiple imputation with chained equations and 50 imputation cycles [8]. All statistical analysis was performed using software (STATA 12.0 StataCorp, College Station, Texas, USA).

3. Results

In total, 398 patients with chronic pruritus and no prior dermatologic diagnoses developed a malignancy within 5 years of their chronic pruritus diagnosis and 8346 patients with chronic pruritus and no prior dermatologic diagnoses did not develop a malignancy within 5 years of their chronic pruritus diagnosis (Table 1). The patients who developed malignancies were older than the patients who did not develop malignancies (70.98 years vs. 60.73 years $p < 0.001$). The percentage of male patients was higher in patients who developed malignancy (46.7% vs 37.2%, $p < 0.001$). The median time to cancer diagnosis after chronic pruritus diagnosis was 1.98 years (standard deviation 1.45). Rates of depression, anxiety, and thyroid disease were the same between these two groups, but patients who developed a malignancy had higher rates of diabetes ($p = 0.03$), renal ($p = 0.03$) and liver disease ($p = 0.03$). There were no differences in Townsend scores, a means of measuring socioeconomic status. More patients who developed a malignancy were ex-smokers or current smokers ($p < 0.001$); however, there was a large amount of missing data and more missing data in those patients who did not develop a malignancy ($p = 0.05$). Alcohol use was similar among the two groups, but again large amounts of data were missing (68.3 and 73.1%). To assess whether age, sex, diabetes, renal and liver disease were risk factors for developing a malignancy in patients with chronic pruritus, multivariable logistic regression was performed (Table 2). Age was transformed into a dichotomous variable (<60 years and ≥60 years) for this analysis. Predictors of malignancy development in patients with chronic pruritus after adjusting for all factors in the model included age ≥60 years (OR 4.04, 95% CI 3.08, 5.31), male sex (OR 1.39, 95% CI 1.13, 1.71), and liver disease (OR 2.37, 95% CI 1.00, 5.65). To include smoking status in our model, an exploratory analysis with multiple imputation via chained equations was carried out (Table 3). In this model predictors of malignancy development in patients with chronic pruritus after adjusting for all factors in the model again included age greater than 60 years (OR 4.13, 95% CI 3.15, 5.42), male sex (OR 1.26, 95% CI 1.02, 1.55), and current or prior smoking (OR 2.02, 95% CI 1.42, 2.88). Liver disease was no longer a statistically significant predictor.

In our prior study, hematological malignancy and cholangiocarcinoma were the only malignancies that were statistically significantly increased in patients with chronic pruritus compared to their age, sex and practice-matched controls [3]. Therefore, in this study we focused on assessing risk factors associated with the development of hematological malignancies and cholangiocarcinoma. There were 61 patients with chronic pruritus and no previous dermatologic codes who developed a hematological malignancy within the 5 year observation period (Table 4). Compared to patients with chronic pruritus and no prior dermatologic codes who did not develop a hematologic malignancy, patients with chronic pruritus and no prior dermatologic codes who did developed a hematologic malignancy were older (71.6 years vs 61.1 years $p < 0.001$). No differences were found in sex proportions, covariates or confounders. The median time to hematological malignancy diagnosis after chronic pruritus diagnosis was 1.71 years (SD 1.44) (Fig. 1). Ten patients with chronic

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