Published in final edited form as:

J Am Acad Dermatol. 2014 April ; 70(4): 651–658. doi:10.1016/j.jaad.2013.11.045.

5-year malignancy incidence in chronic pruritus patients: A population-based cohort study aimed at limiting unnecessary screening practices

Nicole Fett, MD^{1,2}, Kevin Haynes, PharmD, MSCE³, Kathleen Joy Probert, ScD³, and David J. Margolis, MD, PhD²

¹Philadelphia VA Medical Center, Philadelphia, PA

²Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, PA

³Department of Biostatistics and Epidemiology, Center for Clinical Epidemiology and Biostatistics, Center for Pharmacoeconomics Research and Training, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

Background—The incidence of malignancy in patients with chronic pruritus and non-diseased skin is unknown.

Objective—To assess the hazard ratio (HR) of incident overall malignancy and incident malignancy by subtype in patients with chronic pruritus during the 5 years after diagnosis.

Methods—A population-based cohort study was performed in The Health Improvement Network (THIN). 8744 patients with chronic pruritus were matched with 31,580 patients without chronic pruritus based on sex, age, and practice. Primary outcomes were HR of incident malignancy and HR of malignancy subtypes.

Results—The fully adjusted HR for incident malignancy in patients with chronic pruritus was 1.14 (95% CI 0.98–1.33). The fully adjusted HR for incident hematologic malignancy and incident bile duct malignancy in patients with chronic pruritus was 2.02 (95% CI 1.48–2.75) and 3.73 (95% CI 1.55 – 8.97), respectively. The incidence of hematological malignancy and cholangiocarcinoma in patients with chronic pruritus was 0.0016 and 0.0003 per person year, respectively.

Limitations—Potential for misclassification and detection biases

Conclusions and Relevance—Chronic pruritus without concomitant skin changes is a risk factor for having undiagnosed hematological and bile duct malignancies, but not other malignancies. The overall incidence of these malignancies in patients with chronic pruritus is very low.

© 2013 American Academy of Dermatology, Inc. Published by Mosby, Inc. All rights reserved.

Corresponding author: Nicole Fett, MD, Oregon Health and Sciences University, Department of Dermatology, 3303 SW Bond Avenue, Portland, OR 97239, nmfett325@gmail.com, Tel. 608-345-1238.

Relevant Financial Disclosures and Conflicts of Interest: The authors have no conflicts of interest to declare

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Background

Chronic pruritus, defined as itch lasting for equal to or greater than six weeks, affects 8.4 to 22.6% of the population.^{1–3} Patients with chronic pruritus are divided into clinical and etiologic groups by the International Forum on the Study of Itch.⁴ Clinical classifications are based on the presence or absence of skin disease.⁴ Clinical classification group 1 includes patients with cutaneous diseases, such as eczema or psoriasis, as the etiology of their pruritus; group 2 includes patients with normal skin and pruritus; and group 3 includes patients with chronic scratch lesions and pruritus.⁴ Recommendations by expert groups for additional labs and imaging to determine the etiology of a patient's pruritus are based on their clinical classification (i.e. group 1, 2 or 3).^{4, 5} The patients who make up group 2, patients with normal skin and pruritus, are thought to have systemic, neurologic, or psychogenic etiologies of their itch and first-line recommended work-up includes a thorough history and exam, basic labs and chest X-ray.^{4–6} Malignancy is frequently feared as the lurking etiology of chronic pruritus and therefore recommended second-line work-ups often include computed tomography (CT) imaging.^{4–20} However, CT imaging for malignancy screening is expensive, exposes patients to significant amounts of radiation, leads to additional testing to work up incidental findings, and has not been shown to decrease morbidity or mortality from malignancy other than in patients with high risk of lung cancer.^{21–31}

Given the costs and risks of CT screening for malignancy in low risk populations, our study set out to define the 5 year incidence of overall malignancy and malignancy subtypes in patients with chronic pruritus without concomitant skin findings (group 2 patients) to help physicians make informed decisions about the utility of screening these patients for malignancy.

We conducted a large, population-based cohort study to assess the risk of incident malignancy, incidence of subtypes of malignancies, and incidence of death within 5 years of diagnosis in a cohort of patients with chronic pruritus and normal skin, as compared to their age-, sex-, and practice-matched controls.

METHODS

STUDY DESIGN

Methods conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.³² The Health Improvement Network (THIN) is a population-based longitudinal electronic medical records database that is anonymized for research purposes. THIN contains reliable and valid information on approximately 11 million patients in the UK across over 550 medical practices, followed for an average of 9 years, making it an ideal data source for a cohort study.^{33, 34} General Practitioners (GPs) enter patient demographics, medical diagnoses (coded as READ codes), laboratory results, and prescriptions as part of routine medical care. Data quality assessments are routinely carried out and GPs are incentivized to improve data quality.³³ THIN data from 1995 to 2012 were used in this study.

Using the THIN database, we conducted a population-based cohort study of adults greater than 18 years of age with chronic pruritus and without concomitant skin findings (the exposed cohort) versus patients without chronic pruritus (the unexposed cohort).

This study was approved by the University of Pennsylvania Institutional Review Board and the THIN Scientific Review Committee.

STUDY POPULATION, EXPOSURE, AND OUTCOME DEFINITION

Chronic pruritus was defined as having at least two READ codes for generalized pruritus separated by at least 6 weeks. The enrollment date was the date on which a READ code for generalized pruritus that was separated by 6 weeks or more from a prior READ code for generalized pruritus. To ensure that the exposed patients had chronic pruritus with normal skin (i.e. group 2 patients), patients were excluded if they had any READ codes for dermatologic disorders associated with pruritus (e.g. rash, psoriasis, eczema, xerosis) or secondary scratch lesions (e.g. prurigo) prior to the enrollment date. Exposed patients (patients with chronic pruritus without concomitant skin changes) were eligible for the cohort if they were 18 years of age or older at the enrollment date, and had participated in THIN for 6 months or more at the time of enrollment.

As this study was focused on incident malignancy, patients were also excluded if they had any READ codes for malignancy (with the exception of non-melanoma skin cancers) prior to the enrollment date.

To construct an unexposed comparison group, each exposed patient was randomly matched to up to 4 patients without chronic pruritus and without prior READ codes for malignancy who were of the same sex, age (± 3 years), and treated in the same practice for a minimum of 6 months prior to the enrollment date. The unexposed enrollment date is the enrollment date of their exposed counterpart. All patients were followed until they transferred out of the practice, died, developed a malignancy, or reached the end of the study period (5 years).

The primary outcomes, development of any systemic malignancies and malignancy subtypes, were defined by specific READ codes noting malignancy. The incidence of READ code entry for cancer and cancer sub-types is within 10% unity of the standardized incidence ratios (SIR) using age- and sex-specific rates from the UK cancer registry for the corresponding years.^{35, 36} Death was defined by specific READ codes within the patient, medical and administration files denoting death and/or codes indicating transfer out of practice due to death.³⁷

SAMPLE SIZE AND POWER ESTIMATES

All patients with chronic pruritus who met our inclusion and exclusion criteria were included in the study, resulting in an exposed population of 8,744 patients and an unexposed population of 31,580 patients. This sample size ensures that a hazard ratio (HR) of 1.04 with 90% power is detectable, assuming a 2-sided, 0.05 α level test.

IDENTIFICATION OF CONFOUNDERS

Confounders are covariates that are associated with the exposure (chronic pruritus) and the outcome (development of malignancy). Two readily apparent potential confounders, age (prior data suggests that older patients have more problems with pruritus and older age is associated with the development of malignancy) and sex (men in the UK have higher incident cancer rates and data suggests that men are less likely than women to report chronic pruritus), were matched between exposed and unexposed groups to decrease their effect on hazard ratio estimates. Exposed and unexposed were also matched on practice site to ensure they were followed by similar doctors during similar time periods to minimize bias.³⁸

COVARIATES OF INTEREST

All covariates of interest, with the exception of Townsend score, were measured prior to enrollment date. The Townsend score entered closest to enrollment date was utilized. The following additional covariate information was evaluated in this study: liver disease, renal

disease, diabetes, thyroid disease, depression, anxiety, smoking, alcohol use, and body mass index.

STATISTICAL ANALYSIS

Descriptive statistics were performed to summarize and compare patient demographics and the baseline covariates of interest using Pearson's χ^2 test for dichotomous variables and t-tests for continuous variables. Kaplan-Meier estimates were used to estimate time to the development of systemic malignancy, time to development of malignancy subtypes, and time to death between groups. Observation time began on the enrollment date. In models assessing time to malignancy, censoring occurred when patients transferred out of the practice, died, or reached the end of the study period (5 years after enrollment). In models assessing time to death, censoring occurred when patients transferred out of the practice or reached the end of the study period.

The unadjusted hazard ratios for systemic malignancy, malignancy subtypes, and death for exposed patients relative to unexposed were estimated using Cox Proportional Hazards regression analysis. We then built models with hypothesized confounders using a forward selection process. Exposed and unexposed patients were matched on age ± 3 years, therefore age was included in the model as a continuous variable. Although exposed and unexposed were matched on sex and within 2.5% of each other, given the large amount of data the difference was statistically significant and therefore sex was included in the models. Each covariate in the model was checked for proportionality. Covariates were considered confounders if they changed the hazard ratio of the exposure by at least 10%. Model fit was assessed with graphical inspection of Schoenfeld residuals, margins, and deviations using standard methods. Smoking status and alcohol use had large percentages of missing data. Multiple imputation with chained equations and 50 imputation cycles was used to impute this data for exploratory analyses.³⁹ Assessment of risk of incident malignancy by subtype required multiple testing. Bonferroni correction was used to adjust p-values for these analyses. All statistical analysis was performed using STATA 12.0 (College Station, Texas, USA).

RESULTS

We identified 8,744 patients with chronic pruritus without concomitant skin findings (the exposed group) and 31,580 age, sex and practice-matched patients without chronic pruritus (the unexposed group). Patients with chronic pruritus and without concomitant skin findings had a higher prevalence of renal disease, liver disease, thyroid disease, diabetes, depression, and anxiety prior to enrollment date compared to patients without chronic pruritus (Table 1). Patients with chronic pruritus also used more alcohol, smoked more, had higher body mass indices, and were of lower socioeconomic status prior to enrollment date than patients without chronic pruritus (Table 1). The incidence of overall malignancy in exposed and unexposed was 0.0107 and 0.0097 per person year, respectively (Table 2). The incidence of hematological malignancy in exposed and unexposed was 0.0016 and 0.0008 per person year, respectively (Table 2). The incidence of cholangiocarcinoma in exposed and unexposed was 0.0003 and 0.0001 per person year, respectively (Table 2). The incidence of death in exposed and unexposed was 0.0225 and 0.0178 per person year, respectively (Table 2).

In unadjusted analysis, the risk of incident malignancy was the same in patients with chronic pruritus and those without chronic pruritus (HR 1.10, 95% CI 0.99 – 1.23) (Table 3). In a model fully adjusted for sex, age, liver disease, renal disease, diabetes, and smoking, the risk of incident malignancy was the same between groups (HR 1.14, 95% CI 0.98–1.33) (Table

3). Exploratory analysis with multiple imputation of missing values for smoking revealed a stable hazard ratio (HR 1.11, 95% CI 0.99–1.24) (Table 3).

A priori malignancies were divided into major subsets (*e.g.* breast, colon, hematologic, etc). Hematological and bile duct carcinomas were the only subtypes of malignancy with an increased incidence in patients with chronic pruritus. These findings remained significant after p-value adjustment for multiple comparisons. In unadjusted analysis, the risk of incident hematological malignancy was increased in patients with chronic pruritus (HR 1.99, 95% CI 1.46–2.72) (Table 4). In a fully adjusted model including age and sex, the hazard ratio remained elevated (HR 2.02, 95% CI 1.48 – 2.75) (Table 4). Similarly, in unadjusted analysis the risk of incident bile duct carcinoma was increased in patients with chronic pruritus (HR 3.67, 95% CI 1.53–8.83) (Table 4). In a fully adjusted model including age, the hazard ratio remained elevated (HR 3.73, 95% CI 1.55–8.97) (Table 4).

In unadjusted analysis, the risk of death was increased in the patients with chronic pruritus (HR 1.27, 95% CI 1.17 – 1.37) (Table 5). In a fully adjusted model including sex, age, liver disease, renal disease, thyroid disease, diabetes, smoking, alcohol use, and Townsend score, the risk of death remained elevated, but not statistically significant, likely due to the dramatic decrease in observations secondary to missing data (HR 1.13, 95% CI 0.96 – 1.33) (Table 5). In a model excluding alcohol use and smoking data to increase sample size, the risk of death was again elevated (HR 1.22, 95% CI 1.13–1.32). In an exploratory analysis including imputed smoking and alcohol use, the hazard ratio remained elevated (HR 1.19, 95% CI 1.10 – 1.29) (Table 5).

DISCUSSION

Our study suggests that chronic pruritus without coded concomitant skin changes is not an indicator of increase risk of an undetected malignancy overall, but may be an indicator of increased risk of undetected hematological and bile duct malignancies. These data confirms the findings of a previously published uncontrolled longitudinal study of patients with chronic pruritus that found no increased incidence of overall malignancy, but an increased incidence of hematologic malignancies compared to the expected incidence in the general population.¹² Mechanistically, patients with undiagnosed bile duct malignancies (cholangiocarcinoma) are likely developing hyperbilirubinemia, which is driving their pruritus. Over 90% of patients with cancer of the bile ducts will present with jaundice.⁴⁰ Abdominal pain (50%) and weight loss (50%) are also common on presentation.⁴⁰ Although the hazard ratio for incident cholangiocarcinoma was statistically significant, the overall incidence of cholangiocarcinoma in patients with chronic pruritus was very low (0.0003 per person year). Therefore we recommend that screening for cholangiocarcinoma in this patient population be limited to those patients who are jaundiced, or who have hyperbilirubinemia, abdominal pain and unexplained weight loss. Screening for cholangiocarcinoma can be performed with an abdominal ultrasound (US). US is able to correctly diagnosis the cause of obstructive jaundice with 94% sensitivity and 96% specificity.⁴¹ US is relatively inexpensive, does not expose patients to radiation, and has a very low incidence of incidental findings.^{31, 41}

Patients with undiagnosed hematologic malignancies may be pruritic from the release of histamine, leukopeptidases, bradykinine and IL-31 from malignant cells.^{42, 43} Patients with hematologic malignancies present with palpable lymphadenopathy, mediastinal masses, hepatosplenomegaly, “B” symptoms (fevers, drenching night sweats, and unexplained weight loss), or complete blood count (CBC) abnormalities. Although the hazard ratio for incident hematological malignancies was statistically significant, the overall incidence of hematological malignancies in patients with chronic pruritus was very low (0.0016 per

person year). To date, there are no accepted screening tests for hematologic malignancies. A logical approach for screening for hematologic malignancy in a patient with chronic pruritus would include a review of systems for “B” symptoms, a physical exam with emphasis on the lymph nodes, spleen and liver, a CBC and a chest x-ray, as previously advised by an expert panel.⁵

Patients with chronic pruritus without concomitant skin findings also had increased risk of death during our 5 year study period compared to their age-, sex-, and practice-matched controls. Patients with chronic pruritus had more co-morbidities and poorer health practices than their matched controls. Therefore chronic pruritus may serve as a marker of being unwell in general, and is unlikely to lie directly in the causal pathway for death.

Our study does have limitations. A limitation common to any study utilizing a database populated by clinically gathered data (such as THIN) is the reliance on practitioners to correctly enter data. The practitioners entering data are not coding for research purposes; therefore, key information related to study hypotheses may be missing. Patients were not required to see a dermatologist for their diagnosis of pruritus. Given that pruritus is a symptom, and not a skin disease, we are confident that GPs are capable of coding pruritus as a diagnosis. Chronic pruritus has not been validated in THIN, potentially causing misclassification bias. The READ codes used to define malignancy and systemic diseases have been routinely used in previous publications;^{35, 44–46} however, not all have been validated in THIN, also potentially causing misclassification bias. Patients with chronic pruritus may have had an increased number of studies assessing for systemic diseases and systemic malignancy than their age, sex, and practice-matched controls without pruritus, resulting in detection bias. Lastly, a large percentage of data on smoking and alcohol use covariates were missing. However, in models that we strongly felt smoking and alcohol data were essential, we carried out exploratory analyses using multiple imputation of these covariates and our hazard ratio estimates remained stable.

In conclusion, this population-based cohort study demonstrated that chronic pruritus without concomitant skin changes is a risk factor for having undiagnosed hematological and bile duct malignancies. These patients are not at increased risk of being diagnosed with other malignancies. Although the hazard ratios for incident bile duct and hematological malignancies in patients with chronic pruritus without coded skin changes was statistically significant, the incidences of these malignancies were very low (0.0003 and 0.0016 per person year respectively). Broad screening for malignancy in patients with chronic pruritus without concomitant skin findings is unnecessary. Screening for malignancy in patients with chronic pruritus and normal skin should be limited to those patients with signs and symptoms of malignancy detected with a thorough review of symptoms, physical exam, complete blood count and comprehensive metabolic panel.

Acknowledgments

Funding/Support: The project described was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1TR000003.

Role of the Sponsors: This manuscript does not have sponsors

References

1. Weissshaar E, Dalgard F. Epidemiology of itch: adding to the burden of skin morbidity. *Acta Derm Venereol.* 2009; 89:339–50. [PubMed: 19688144]

2. Mattered U, Strassner T, Apfelbacher CJ, Diepgen TL, Weisshaar E. Measuring the prevalence of chronic itch in the general population: development and validation of a questionnaire for use in large253 scale studies. *Acta Derm Venereol.* 2009; 89:250–6. [PubMed: 19479120]
3. Mattered U, Apfelbacher CJ, Vogelgsang L, Loerbroks A, Weisshaar E. Incidence and Determinants of Chronic Pruritus: A Population-based Cohort Study. *Acta Derm Venereol.* 2013
4. Stander S, Weisshaar E, Mettang T, Szepletowski JC, Carstens E, Ikoma A, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. *Acta Derm Venereol.* 2007; 87:291–4. [PubMed: 17598029]
5. Weisshaar E, Szepletowski JC, Darsow U, Misery L, Wallengren J, Mettang T, et al. European guideline on chronic pruritus. *Acta Derm Venereol.* 2012; 92:563–81. [PubMed: 22790094]
6. Steinhoff M, Cevikbas F, Ikoma A, Berger TG. Pruritus: management algorithms and experimental therapies. *Semin Cutan Med Surg.* 2011; 30:127–37. [PubMed: 21767775]
7. Zirwas MJ, Seraly MP. Pruritus of unknown origin: a retrospective study. *J Am Acad Dermatol.* 2001; 45:892–6. [PubMed: 11712035]
8. Lyell A. The itching patient. A review of the causes of pruritus. *Scott Med J.* 1972; 17:334–7. [PubMed: 4562884]
9. Rajka G. Investigation of patients suffering from generalized pruritus, with special references to systemic diseases. *Acta Derm Venereol.* 1966; 46:190–4. [PubMed: 4162639]
10. Polat M, Oztas P, Ilhan MN, Yalcin B, Alli N. Generalized pruritus: a prospective study concerning etiology. *Am J Clin Dermatol.* 2008; 9:39–44. [PubMed: 18092842]
11. Gilchrist BA. Pruritus: pathogenesis, therapy, and significance in systemic disease states. *Arch Intern Med.* 1982; 142:101–5. [PubMed: 7032441]
12. Paul R, Jansen CT. Itch and malignancy prognosis in generalized pruritus: a 6-year follow-up of 125 patients. *J Am Acad Dermatol.* 1987; 16:1179–82. [PubMed: 3597859]
13. Kantor GR, Lookingbill DP. Generalized pruritus and systemic disease. *J Am Acad Dermatol.* 1983; 9:375–82. [PubMed: 6630598]
14. Ayyamperumal A, Tharini G, Ravindran V, Parveen B. Cutaneous manifestations of internal malignancy. *Indian J Dermatol.* 2012; 57:260–4. [PubMed: 22837557]
15. Rajagopal R, Arora PN, Ramasastry CV, Kar PK. Skin changes in internal malignancy. *Indian J Dermatol Venereol Leprol.* 2004; 70:221–5. [PubMed: 17642619]
16. Grundmann S, Stander S. Chronic pruritus: clinics and treatment. *Ann Dermatol.* 2011; 23:1–11. [PubMed: 21738356]
17. Chiang HC, Huang V, Cornelius LA. Cancer and itch. *Semin Cutan Med Surg.* 2011; 30:107–12. [PubMed: 21767772]
18. Yosipovitch G. Chronic pruritus: a paraneoplastic sign. *Dermatol Ther.* 2010; 23:590–6. [PubMed: 21054705]
19. Sher TH. Clinical evaluation of generalized pruritus. *Compr Ther.* 1992; 18:14–9. [PubMed: 1424535]
20. Raap U, Stander S, Metz M. Pathophysiology of itch and new treatments. *Curr Opin Allergy Clin Immunol.* 2011; 11:420–7. [PubMed: 21772138]
21. Jacobs PC, Mali WP, Grobbee DE, van der Graaf Y. Prevalence of incidental findings in computed tomographic screening of the chest: a systematic review. *J Comput Assist Tomogr.* 2008; 32:214–21. [PubMed: 18379305]
22. Messersmith WA, Brown DF, Barry MJ. The prevalence and implications of incidental findings on ED abdominal CT scans. *Am J Emerg Med.* 2001; 19:479–81. [PubMed: 11593466]
23. Thompson RJ, Wojcik SM, Grant WD, Ko PY. Incidental Findings on CT Scans in the Emergency Department. *Emerg Med Int.* 2011:624847. [PubMed: 22046542]
24. Smith-Bindman R, Lipson J, Marcus R, Kim KP, Mahesh M, Gould R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med.* 2009; 169:2078–86. [PubMed: 20008690]
25. Amis ES Jr, Butler PF, Applegate KE, Birnbaum SB, Brateman LF, Hevezi JM, et al. American College of Radiology white paper on radiation dose in medicine. *J Am Coll Radiol.* 2007; 4:272–84. [PubMed: 17467608]

26. Priola AM, Priola SM, Gaj-Levra M, Basso E, Veltri A, Fava C, et al. Clinical implications and added costs of incidental findings in an early detection study of lung cancer by using low-dose spiral computed tomography. *Clin Lung Cancer*. 2013; 14:139–48. [PubMed: 22868220]
27. Bromage SJ, Liew MP, Moore KC, Raju B, Shackley DC. The economic implications of unsuspected findings from CT urography performed for haematuria. *Br J Radiol*. 2012; 85:1303–6. [PubMed: 22573297]
28. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011; 365:395–409. [PubMed: 21714641]
29. Vansteenkiste J, Doooms C, Mascaux C, Nackaerts K. Screening and early detection of lung cancer. *Ann Oncol*. 2012; 23 (Suppl 10):x320–7. [PubMed: 22987984]
30. Furtado CD, Aguirre DA, Sirlin CB, Dang D, Stamato SK, Lee P, et al. Whole-body CT screening: spectrum of findings and recommendations in 1192 patients. *Radiology*. 2005; 237:385–94. [PubMed: 16170016]
31. Orme NM, Fletcher JG, Siddiki HA, Harmsen WS, O’Byrne MM, Port JD, et al. Incidental findings in imaging research: evaluating incidence, benefit, and burden. *Arch Intern Med*. 2010; 170:1525–32. [PubMed: 20876402]
32. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology*. 2007; 18:800–4. [PubMed: 18049194]
33. Data CS. THIN Data Quality Assurance. <http://csdmruk.cegedim.com2013>
34. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care*. 2011; 19:251–5. [PubMed: 22828580]
35. Haynes K, Forde KA, Schinnar R, Wong P, Strom BL, Lewis JD. Cancer incidence in The Health Improvement Network. *Pharmacoepidemiol Drug Saf*. 2009; 18:730–6. [PubMed: 19479713]
36. Iyen-Omofoman B, Hubbard RB, Smith CJ, Sparks E, Bradley E, Bourke A, et al. The distribution of lung cancer across sectors of society in the United Kingdom: a study using national primary care data. *BMC Public Health*. 2011; 11:857. [PubMed: 22074413]
37. Hall GC. Validation of death and suicide recording on the THIN UK primary care database. *Pharmacoepidemiol Drug Saf*. 2009; 18:120–31. [PubMed: 19109801]
38. Haynes K, Bilker WB, Tenhave TR, Strom BL, Lewis JD. Temporal and within practice variability in the health improvement network. *Pharmacoepidemiol Drug Saf*. 20:948–55. [PubMed: 21755569]
39. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res*. 2007; 16:199–218. [PubMed: 17621468]
40. Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg*. 1996; 224:463–73. discussion 73–5. [PubMed: 8857851]
41. Sharma MP, Ahuja V. Aetiological spectrum of obstructive jaundice and diagnostic ability of ultrasonography: a clinician’s perspective. *Trop Gastroenterol*. 1999; 20:167–9. [PubMed: 10769604]
42. Ishii T, Wang J, Zhang W, Mascarenhas J, Hoffman R, Dai Y, et al. Pivotal role of mast cells in pruritogenesis in patients with myeloproliferative disorders. *Blood*. 2009; 113:5942–50. [PubMed: 19196660]
43. Krajnik M, Zylicz Z. Pruritus in advanced internal diseases. Pathogenesis and treatment. *Neth J Med*. 2001; 58:27–40. [PubMed: 11137748]
44. Ogdie A, Haynes K, Troxel AB, Love TJ, Hennessy S, Choi H, et al. Risk of mortality in patients with psoriatic arthritis, rheumatoid arthritis and psoriasis: a longitudinal cohort study. *Ann Rheum Dis*. 2013
45. Azfar RS, Seminara NM, Shin DB, Troxel AB, Margolis DJ, Gelfand JM. Increased risk of diabetes mellitus and likelihood of receiving diabetes mellitus treatment in patients with psoriasis. *Arch Dermatol*. 2012; 148:995–1000. [PubMed: 22710320]

46. Denburg MR, Haynes K, Shults J, Lewis JD, Leonard MB. Validation of The Health Improvement Network (THIN) database for epidemiologic studies of chronic kidney disease. *Pharmacoepidemiol Drug Saf.* 2011; 20:1138–49. [PubMed: 22020900]

Patients with chronic pruritus and normal skin have systemic, neurologic, or psychogenic itch etiologies

5 year risk of diagnosis of hematological or bile duct malignancy is elevated in these patients, without an increased risk of other malignancies

Screening practices should be limited to evaluation for bile duct and hematologic malignancies.

Table 1

Characteristics of Study Groups

Characteristics	Exposed (chronic pruritus)	Unexposed	P-value
Qualifying patients	8,744	31,580	
Age at enrollment, yrs Mean (SD)	61.19 (18.90)	61.64 (18.57)	0.05
Sex	M = 3,288 (37.60%) F = 5,456 (62.40%)	M = 11,118 (35.21%) F = 20,462 (64.79%)	<0.001
Transfer from practice	2,612 (29.87%)	8,387 (26.56%)	<0.001
Patient death	852 (9.74%)	2,477 (7.84%)	<0.001
Covariates			
Liver disease	57 (0.65%)	38 (0.12%)	<0.0013
Renal disease	327 (3.74%)	743 (2.35%)	<0.0013
Depression	667 (7.63%)	1,335 (4.23%)	<0.0013
Anxiety	373 (4.26%)	672 (2.13%)	<0.0013
Thyroid disease	165 (1.89%)	365 (1.16%)	<0.0013
Diabetes	905 (10.35%)	2,507 (7.94%)	<0.0013
Confounders			
Smoking			
Non-smoker	1,764 (39.53%)	5,988 (43.07%)	<0.001
Ex-smoker	1,411 (31.62%)	3,992 (28.71%)	
Current smoker	1,286 (28.83%)	3,924 (28.22%)	
Missing	4,283 (49%)	17,676 (56%)	<0.001
BMI			
Normal	1,161 (32.48)	3,516 (33.08%)	<0.001
Overweight	2,323 (65.00%)	6,888 (64.80%)	
Underweight	90 (2.52%)	226 (2.13%)	
Missing	5,170 (59.12%)	20,950 (66.34%)	<0.001
Alcohol Use			
None	551 (23.26%)	1,381 (19.27%)	<0.001
Some	1,817 (76.74%)	5,784 (80.73%)	
Missing	6,376 (73%)	24,415 (77.31%)	
Townsend Score			
0	264 (3.05%)	838 (2.68%)	<0.001

Characteristics	Exposed (chronic pruritus)	Unexposed	P-value
1	1,860 (21.46%)	7,650 (24.44%)	
2	1,646 (18.99%)	6,587 (21.05%)	
3	1,659 (19.14%)	6,175 (19.73%)	
4	1,771 (20.43%)	5,624 (17.97%)	
5	1,439 (16.60%)	4,317 (13.79%)	
9	30 (0.35%)	108 (0.35%)	
Missing	75 (0.86%)	281 (0.89%)	0.05

Table 2

Incidences of Outcomes

Outcome		Incidence
Incident Malignancy	Exposed	0.0107
	Unexposed	0.0097
Hematological Malignancy	Exposed	0.0016
	Unexposed	0.0008
Cholangiocarcinoma	Exposed	0.0003
	Unexposed	0.0001
Death	Exposed	0.0225
	Unexposed	0.0178

Table 3

Hazard ratio of incident malignancy and exploratory analysis

Characteristics	# obs	Incident malignancy, HR (95% CI)
Incident Systemic Malignancy: total = 1729		
Unadjusted model	40,324	1.10 (0.99 – 1.23)
Incident Systemic Malignancy: total = 851		
Original model*	18,365	1.14 (0.98 – 1.33)
Parsimonious model (sex, age, smoking)	18,365	1.15 (0.99 – 1.34)

• Adjusted for sex, age, liver, renal, diabetes, anxiety, depression, smoking

Table 4

Hazard ratio of hematological malignancy and bile duct carcinoma

Characteristics	# obs	Incident HR (95%)
Hematologic Malignancy: total = 174		
Unadjusted hematologic malignancy model	40,324	1.99 (1.46 – 2.72)
Adjusted hematologic malignancy model (age and sex)	40,324	2.02 (1.48 – 2.75)
Bile Duct Carcinoma: total = 20		
Unadjusted bile duct carcinoma model	40,324	3.67 (1.53 – 8.83)
Adjusted bile duct carcinoma model (including age)	40,324	3.73 (1.55 – 8.97)

Table 5

Hazard ratio of death and sensitivity analysis

Characteristics	# obs	Incident malignancy, HR (95% CI)
Deaths: total = 3329		
Unadjusted model	40,324	1.27 (1.17 – 1.37)
Original model* (Deaths = 745)	8902	1.13 (0.96 – 1.33)
Model without etoh and smoking (Deaths = 3308)	39,968	1.21 (1.11 – 1.30)
Model without etoh, smoking, or townsend	40,324	1.22 (1.13 – 1.32)
Exploratory model with imputation of smoking and etoh	40,324	1.19 (1.10 – 1.29)

- Adjusted for age, sex, liver disease, renal disease, thyroid disease, diabetes mellitus, townsend score, smoking, alcohol use