# Association between psoriasis and incident cancer: the Iowa's Women's Health Study

**Anna E. Prizment**,
Division of Epidemiology and Community Health, University of Minnesota, 1300 2nd Street South, Suite 300, Minneapolis, MN 55455, USA

**Alvaro Alonso**,
Division of Epidemiology and Community Health, University of Minnesota, 1300 2nd Street South, Suite 300, Minneapolis, MN 55455, USA

**Aaron R. Folsom**,
Division of Epidemiology and Community Health, University of Minnesota, 1300 2nd Street South, Suite 300, Minneapolis, MN 55455, USA

Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA

**Rehana L. Ahmed**,
Department of Dermatology, University of Minnesota, Minneapolis, MN, USA

**Beth A. Virnig**,
Division of Health Policy and Management, University of Minnesota, Minneapolis, MN, USA

**Erin M. Warshaw**, and
Department of Dermatology, University of Minnesota, Minneapolis, MN, USA

Department of Dermatology, VA Medical Center, Minneapolis, MN, USA

**Kristin E. Anderson**
Division of Epidemiology and Community Health, University of Minnesota, 1300 2nd Street South, Suite 300, Minneapolis, MN 55455, USA

Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA

Anna E. Prizment: prizm001@umn.edu

## Abstract

**Introduction**—Studies have reported higher cancer risk in individuals with psoriasis, a chronic inflammatory autoimmune disease; however, adjustment for potential confounders was lacking.

**Methods**—We examined the association of psoriasis with cancer incidence in 32,910 women after age 65 in the IWHS cohort linked to Medicare. Psoriasis was defined as: 2+ psoriasis claims from any Medicare file during 1991–2004 or 1+ psoriasis claim from a dermatologist ($n = 719$). Severe psoriasis was defined as 4+ psoriasis claims from a dermatologist in any year ($n = 121$). Cox proportional hazards regression, with psoriasis as a time-dependent variable was conducted to calculate hazard ratios (HR) and 95% confidence intervals (CI) of total ($n = 6,488$), breast ($n = 2,066$), lung ($n = 742$), and colon cancers ($n = 947$).

**Results**—With age-adjustment, psoriasis (yes vs. no) was associated with increased risk of lung
1.9 (95% CI: 1.2–3.0), colon 1.6 (95% CI: 1.1–2.5), and total cancer 1.2 (95% CI, 1.0–1.4). After
further adjustment for smoking, body mass index, education, physical activity, and hormone
therapy use, only the association for colon cancer remained statistically significant (HR = 1.6,
95% CI: 1.0–2.4) and was stronger for severe psoriasis.

**Conclusion**—The observed association between psoriasis and colon cancer may reflect
inflammatory or unidentified processes.

### Keywords

Colon cancer; Inflammation; Psoriasis; Immune disease; Medicare

## Introduction

Psoriasis is among the most common inflammatory autoimmune diseases of the skin;
prevalence is 1–3% in the United States, and approximately 7.5 million people are affected
[1]. Onset peaks in young adulthood and again at age 60, but psoriasis can begin at any age
and last a lifetime [2, 3]. Psoriasis with an early age at onset is thought to be hereditary and
is often associated with human leukocyte antigen (HLA-Cw6), whereas psoriasis that starts
in older age is sporadic [4, 5]. Most psoriasis is managed with topical therapies. However,
approximately 25% of patients have moderate to severe psoriasis which requires treatment
with phototherapy, systemic agents, and/or immunomodulators. There is mounting evidence
that people with more severe psoriasis have increased incidence of cardiovascular disease,
hypertension, diabetes, and cancer [6]. Many studies showed that psoriasis is positively
associated with increased risk of lymphoma and non-melanoma skin cancer [3, 7–13]. Far
fewer studies focused on solid organ cancers; reported observations include positive
associations with lung, colorectal, breast, pancreas and some other cancers [7, 8]. The main
limitation of those studies was potential bias due to the lack of adjustment for potential
confounding factors. To our knowledge, only one prior study on psoriasis and cancer
controlled for potential confounders [9].

Furthermore, most studies of psoriasis and cancer have involved specific groups of patients
either hospitalized with psoriasis [7, 8, 11–13] or those treated with phototherapy or
systemic medications [14–16]. We sought to address limitations of previous studies in the
current study.

We hypothesized that psoriasis is associated with the risk of total cancers as well as solid
organ cancers including breast, lung, and colon in a population-based cohort of elderly Iowa
women, after adjusting for potential confounders. We hypothesized that the strongest
association would be with colon cancer since psoriasis is an inflammatory disease and colon
cancer has been consistently shown to be associated with inflammation. To test these
hypotheses, we identified all women with psoriasis at or after age 65 years using Medicare
data linked to the Iowa Women's Health Study (IWHS) during 1991–2004.

## Materials and methods

This study combined three data sources: the IWHS, Medicare data and the Iowa SEER
cancer registry.

### IWHS study design

Detailed descriptions of IWHS have been published previously [17–19]. Briefly, the IWHS
cohort included 41,836 women aged 55–69 years recruited via a baseline questionnaire

mailed in 1986. Follow-up questionnaires were mailed in 1987, 1989, 1992, and 1997 to update information about participants' residence, vital status, and other characteristics. Deaths were ascertained by annual linkage to Iowa death certificates, supplemented by linkage to the National Death Index for non-respondents and emigrants from Iowa. Emigration rate from Iowa was less than 1% [19]. The University of Minnesota Institutional Review Board approved this study, and all participants gave informed consent.

### IWHS-Medicare linkage

IWHS identifiers were linked to Centers for Medicare Services (CMS) claims data from 1986 until 2004 via social security number, first and last names, and date of birth [20]. Linkage was conducted for participants aged 65+, since Medicare provides payment for health benefits for US residents 65 years and older. The linkage was successful for 99% of the cohort that survived to age 65 ($n = 40,668$).

Information about Medicare participants was collected from four files (Denominator, MedPar, Carrier, and Outpatient files). The annual Denominator file was used to identify periods of enrollment into Medicare and managed care. Information about inpatient services, including discharge codes, has been available since 1986, whereas data about outpatient services, including diagnosis codes, have been available since 1991 (Outpatient and Carrier files). In addition, information about the specialty of providers was obtained from Carrier files. The data about most prescription drugs in the Medicare database was not available until 2006 [20].

### IWHS-Iowa SEER cancer registry linkage

Incident cancer cases from 1991 through 2006 (except for non-melanoma skin cancer) were ascertained via linkage of the IWHS cohort to the State Health Registry of Iowa, a participant in the Surveillance, Epidemiology, and End Results Program (SEER). Sites were defined using ICD-O codes (International Classification of Diseases for Oncology, 3rd ed) [21].

### Analytical cohort

Our goal was to ascertain psoriasis, which is usually treated in a clinic setting and most psoriasis claims are found in the Medicare Carrier file available in 1991–2004. Thus, our analytical sample included only participants who, since 1991, were enrolled in at least 1 month of fee-for-service Part A and Part B Medicare coverage after reaching 65 years ($n = 39,503$). Those participants who did not reside in Iowa at the start of their follow-up were excluded because their cancers would not be identified by SEER ($n = 1,354$). Participants were followed from the start of their follow-up until disenrollment from full Medicare fee-for-service benefits, emigration from Iowa, cancer diagnosis in Iowa, death, or end of follow-up on 31 December 2006, whichever occurred earlier. Further, women who had cancer at baseline or were diagnosed with cancer before the start of their follow-up (except non-melanoma skin cancer) were excluded ($n = 4,883$). After these exclusions, 33,266 women were left in the cohort.

### Psoriasis ascertainment

Psoriasis diagnoses were identified using the International Classification of Diseases (ICD-9) diagnosis code 696.1 in Medicare claims data. This is the only ICD-9 code for psoriasis. In our analytical cohort, there were 1,075 women who had 696.1 code. Only those women with 1+ dermatology claim with a psoriasis diagnosis code or those with 2+ claims on different days at any time during follow-up were included (Fig. 1). Thus, 719 patients among 32,910 women free of cancer (about 2.2%) had a diagnosis of psoriasis at 65+ in

1991–2004 in IWHS/CMS. The prevalence of psoriasis in the cohort prior to excluding cancer was also 2.2%. This agrees with the reported psoriasis prevalence of 1–3% in the United States [1]. Consistent with clinical patterns, 96% of psoriasis cases were identified from Carrier files and 4% from MedPAR or Outpatient files only. Within the Carrier file, 85% of all psoriasis claims were submitted by dermatologists, which is consistent with National Ambulatory Medical Survey data—82% of visits for psoriasis were to dermatologists in 1990–2001 in the United States [22].

We used the number of visits to a dermatologist with a psoriasis diagnostic claim as a surrogate measure of severity. Severe psoriasis was defined as having 4+ visits to a dermatologist in any year ($n = 121$). Four visits were selected as a cut-off because patients on oral medications or UV light treatment are usually seen every 3 months by dermatologists.1 All other cases of psoriasis were considered mild ($n = 598$). We did not have data about psoriasis diagnoses before enrollment in Medicare; thus we examined women who had "active" psoriasis at age 65+ years.

## Other exposure information

The baseline questionnaire (1986) collected information about age, education level, smoking status and pack-years of smoking, anthropometric characteristics, usual alcohol intake within the last year, physical activity level, reproductive history, use of oral contraceptives and hormone therapy (HT) [17, 23]. Information about HT use, diabetes mellitus, heart disease, and hypertension was collected at baseline and each follow-up.

## Cancer ascertainment

In our analytical cohort, there were 6,488 total cancers (excluding non-melanoma skin cancer), 2,066 breast, 742 lung, and 947 colon cancers. Due to insufficient number of cases (less than 10 among psoriatic patients), we were unable to investigate the association of psoriasis with less common neoplasms, such as cancers of the pancreas, bladder, hematopoietic or several others, for which associations were observed in some studies. We also did not have information about non-melanoma skin cancers.

## Statistical analysis

Characteristics of women with and without psoriasis were compared using the chi-square tests and *t* tests for categorical and continuous variables, respectively. Prevalent odds ratio for psoriasis (age- and multivariate-adjusted) for selected characteristics were calculated using logistic regression.

Age-adjusted cancer incidence rates for psoriatic and non-psoriatic groups were compared using Poisson regression. To further investigate the association of "active" psoriasis at 65+ years with each cancer, we used a Cox proportional hazards model with psoriasis as a time-dependent covariate [24].

The following variables, associated with cancer and psoriasis, were included into a multivariate-adjusted model: age at the start of follow-up, BMI, education, smoking status, pack-years, HT use, physical activity, and, for breast cancer, number of live births. Further adjustment for alcohol intake, WHR, history of diabetes, oral contraceptives use, and the start of follow-up did not materially change associations, and these variables were not included in the final model.

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1E. Warshaw, Department of Dermatology, University of Minnesota, October, 2009, personal communication.

We also examined associations between psoriasis "severity" and risk of total and specific cancers by calculating hazard ratios (HR) for each cancer in groups with severe and mild psoriasis versus "no psoriasis," although there was limited power to conduct these analyses. We tested effect modification of the psoriasis—cancer association by smoking and BMI, since these are risk factors for cancer and are related to psoriasis: no interactions were detected ($p = 0.3–0.8$). All analyses were performed using SAS 9.2, all $p$ tests were two-sided.

## Results

The analytical cohort included 32,910 initially cancer-free women with a total of 389,180 person-years of follow-up. Mean age at start of follow-up was 68.1 years and over 99% women were White. Consistent with findings from other studies, psoriasis was positively associated with higher education, smoking, lack of regular physical activity, diabetes, hypertension, and history of HT use (Table 1) [1, 25–29]. We conducted a sensitivity analysis by including into psoriasis group only women with 2+ claims for psoriasis, i.e., women with a more stringent definition for diagnosis, and all the associations were practically unchanged.

Age-adjusted incidence rates of lung, colon, and total cancers were higher for those with psoriasis than for those without (Table 2). Age-adjusted hazard ratios were increased for lung, 1.9 (95% CI: 1.2–3.0); colon, 1.6 (95% CI: 1.0–2.5) and total cancer, 1.2 (95% CI: 1.0–1.4). There was no association between psoriasis and breast cancer (Table 2). After multivariate adjustment, all observed associations were attenuated: hazard ratios of lung, colon, and total cancer were 1.3 (95% CI: 0.8–2.0), 1.6 (95% CI: 1.0–2.4) and 1.1 (95% CI: 0.9–1.4), respectively. This attenuation was largely due to smoking: after adjusting for all the covariates except smoking, hazard ratios for all cancers were virtually the same as in the age-adjusted analyses. Compared to those without psoriasis, hazard ratios of colon cancer were 1.5 for mild and 1.9 for severe psoriasis ($p$ trend = 0.03) (Table 3).

In addition, sensitivity analyses were conducted. To reduce ambiguity for a temporal relation between psoriasis and cancer, we included only women who had at least 2 or 5 years of cancer-free follow-up time. The results were similar to those in the main analysis. For instance, hazard ratios of colon cancer, for psoriatic versus non-psoriatic patients, were 1.6 (95%CI: 1.0–2.4) and 1.84 (95%CI: 1.8–2.9) for those with at least 2 and 5 years of follow-up, respectively.

Further, most of the covariates were ascertained in 1986, while the follow-up started in 1991. Because some of the covariates could have changed during this time gap, we conducted analyses stratified by the median time between 1986 and the start of follow-up (~5 years); similar associations between psoriasis and colon cancer were observed in both subgroups: HR = 1.6 (95% CI: 0.9–2.9) for those with a time gap <5 years and HR = 1.8 (95% CI: 0.9–3.4) for those with a time gap ≥5 years.

Finally, we stratified colon cancer into proximal and distal. The association of psoriasis with proximal colon cancer (HR = 2.0, 95% CI: 1.2–3.1) was stronger than with overall colon cancer. We were unable to examine psoriasis in relation to distal colon cancer due to small case numbers.

## Discussion

In a prospective analysis, having psoriasis at age 65+ was associated with higher subsequent colon cancer risk after adjustment for age, BMI, education, smoking, physical activity, and HT use. The hazard ratio for colon cancer was higher among those with severe compared to

mild psoriasis. We also observed increased age-adjusted hazard ratios for lung and total cancer for psoriatic versus non-psoriatic patients but this was primarily due to confounding by cigarette smoking.

The majority of previous studies of psoriasis and cancer examined total, skin, and lymphoproliferative cancers, whereas only a few studies investigated associations with solid organ cancers. Several cohorts from Scandinavian countries, which included patients of wide age ranges, observed increased standardized incidence ratios (SIR) among psoriatic patients versus the general population for cancers as follows: total (by 27–40%), lung (by 40–110%), and colon (by 30–40%) [7, 8, 11–13]. This increase was largely explained by an excess risk of skin cancer and lymphoproliferative cancers and/or cancers related to smoking. The main limitation of these Scandinavian studies was a potential bias due to lack of data about confounding variables. Another limitation is that those studies included only hospitalized patients, the majority of whom were hospitalized for psoriasis [7, 8, 11]. Such patients likely have more severe psoriasis and, possibly, different cancer risk than other psoriatic patients [30].

Only a few population-based studies have investigated psoriasis in relation to cancer, particularly solid organ cancers. A US study using the Medicaid administrative database reported an increase in total cancer risk by 78% for patients with severe psoriasis (those treated with systemic medication) and by 13% for those with mild disease compared to hypertensive patients [3]. Recently, a nested case–control study by Brauchli et al. [9] was the first to examine a link between psoriasis and cancer after adjusting for confounding variables, such as age, sex, calendar time, BMI, smoking, and benign tumors. In that study, psoriatic patients, 55% of whom were younger than 50 years at the time of psoriasis diagnosis, had slightly increased odds ratio of total cancer (OR = 1.13, 95% CI: 1.02–1.26), which was higher for psoriasis with duration ≥4 years: (OR = 1.50, 95% CI: 1.30–1.74) [9]. The odds ratio for colorectal cancers was also increased with longer-duration psoriasis: (OR ~ 2.5, statistically significant, but exact data were not reported). The results for total and colorectal cancer are in agreement with the findings from the multivariate analysis in our study.

The biological mechanism explaining the relation between psoriasis and cancer is under investigation. Psoriasis is considered a systemic inflammatory disease not limited to the epidermis. It is characterized by immune deregulation: Th1 cells infiltrate the skin of a psoriatic patient and release inflammatory cytokines, such as interleukins (IL-1, IL-6), interferon-$\gamma$, and tumor necrosis factor-$\alpha$, and stimulate dendritic cells, macrophages, and neutrophils, which induce epidermal hyperproliferation and hyperplasia [25, 31–33]. A deregulated immune system together with chronic inflammation may lead to mutations in dividing cells and errors in elimination of malignant cells, resulting in increased risk of cancer, especially, of lymphoproliferative cancers [34, 35].

Several lines of evidence link inflammation to colorectal cancer risk. Colorectal cancer is the only cancer for which the protective effect of an anti-inflammatory drug—aspirin has been clinically established [36]. Several studies reported positive associations between C-reactive protein, a systemic inflammatory marker, and risk of colorectal cancer [37–40]. In addition, positive associations have been shown between inflammatory bowel disease and colorectal cancer [36, 41] and between inflammatory bowel disease and psoriasis [42, 43]. Thus, chronic inflammation associated with psoriasis could result in subsequent colon cancer.

The major strength of our study is use of data from a large prospective population-based cohort linked to the already existing longitudinal Medicare dataset, which allowed for a

cost-efficient analysis. To our knowledge, this is the first attempt to comprehensively establish a diagnosis of psoriasis through Medicare. Ascertainment of psoriasis via Medicare claims is free from usual bias such as non-response or recall. Furthermore, to our knowledge, this is only the second study that examined an association between psoriasis and incident cancers after adjustment for confounding variables.

Our study has limitations. Because we used the Medicare database for psoriasis ascertainment, we cannot exclude the possibility of incomplete coding and coding errors [44, 45]. The precise date of psoriasis onset was also unknown. We did not validate psoriasis diagnosis. However, validation studies conducted for other autoimmune diseases in Medicare, which used medical records as the gold standard, reported high sensitivities of the physician claims (0.90 for rheumatoid arthritis and 0.85 for systemic lupus erythematosus), and high positive predictive values (0.90 for both of these diseases) [44]. Further, we conducted several sensitivity analyses and their results were robust. Finally, the most common diseases that can be misdiagnosed as psoriasis are seborrheic dermatitis and eczematous skin conditions, which are not known to be related to cancer [7].

A limitation in our study is that power was limited for examining colon cancer risk in different subgroups. However, we observed a statistically significant increase in hazard ratio of proximal colon cancer by ~100% for psoriatic versus non-psoriatic patients. An additional limitation is that we lacked data about treatment. Although it is unlikely that systemic drugs or phototherapy affect the risk of solid organ cancers (other than skin cancer), this possibility cannot be fully excluded. Another potential concern is surveillance bias: patients with psoriasis could be more likely screened for cancer. Finally, our study was conducted among white elderly women in Iowa; results may not be generalizable to other age, race, gender, or other geographic settings.

In summary, our analysis showed that there was a positive association between psoriasis and colon cancer incidence. This supports the view that inflammation may play a role in colon carcinogenesis.

## Acknowledgments

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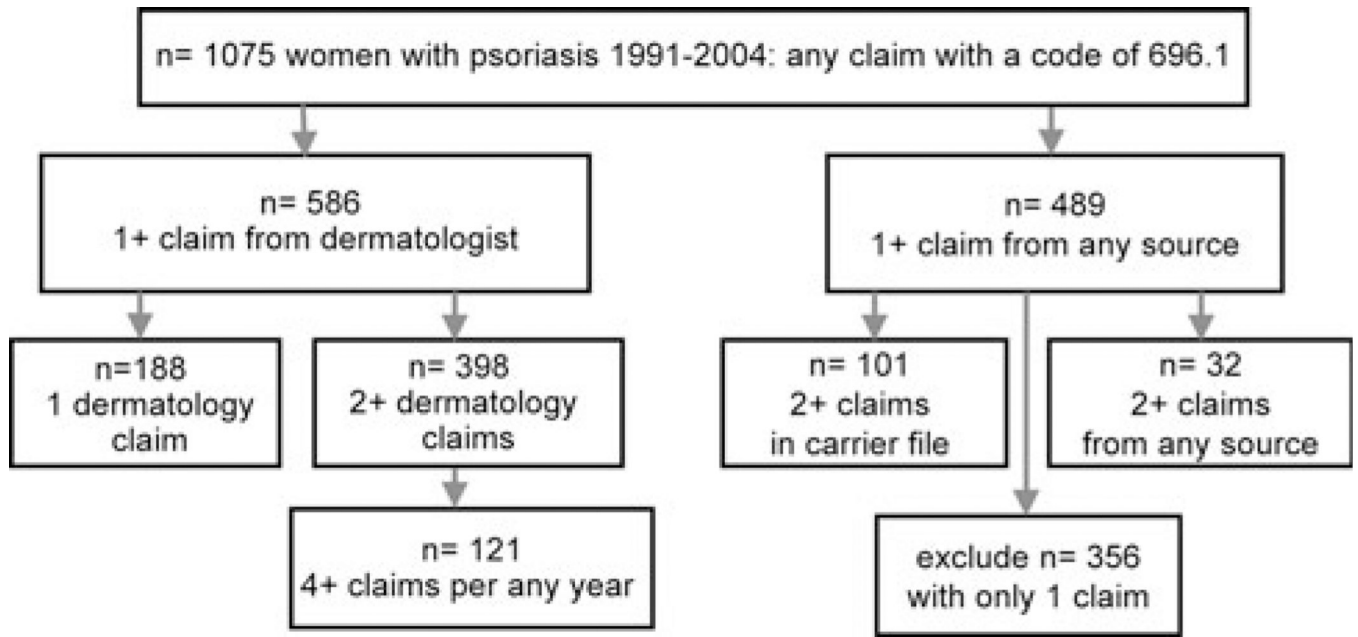**Fig. 1.**
Number of cancer-free women with psoriasis in IWHS/Medicare, 1991–2004 (After
excluding women with only one non-dermatology claim, 719 women with psoriasis
remained in the cohort ($n = 188 + 398 + 101 + 32 = 719$)

**Table 1**

Selected characteristics in relation to psoriasis, IWHS/Medicare, 1991–2004

| Characteristics | No psoriasis $n = 32,191$ (97.8%) | Psoriasis $n = 719$ (2.2%) | Age-adjusted odds ratios[b] of psoriasis (95% CI) | Multivariate-adjusted[b,c] odds ratios of psoriasis (95% CI) |
|---|---|---|---|---|
| Mean age at the start of follow-up ± SD (years) | $68.1 \pm 3.2$[a] | $67.8 \pm 3.0$[a] | 1.0 (0.9–1.0) | |
| BMI categories in 1986 (kg/m²) (%)[d] | | | | |
| <24.9 | 39.5 | 41.3 | 1 | 1 |
| 25–30 | 37.3 | 33.4 | 0.9 (0.7–1.0) | 0.9 (0.7–1.1) |
| ≥30 | 23.2 | 25.3 | 1.0 (0.9–1.3) | 1.1 (0.9–1.4) |
| | | | $p = 0.7$ | $p = 0.3$ |
| Education in 1986 (%)[d] | | | | |
| Less than high school | 19.6 | 17.9 | 1 | 1 |
| High school | 42.2 | 38.2 | 1.0 (0.8–1.2) | 1.0 (0.8–1.3) |
| More than high school | 38.1 | 43.9 | 1.3 (1.0–1.6) | 1.3 (1.0–1.6) |
| | | | $p = 0.03$ | $p = 0.02$ |
| Smoking in 1986 (%)[d] | | | | |
| Never | 67.6 | 53.1 | 1 | 1 |
| Former | 18.6 | 25.0 | 1.4 (1.1–1.8) | 1.4 (1.1–1.7) |
| Current | 13.8 | 22.0 | 1.5 (1.1–2.0) | 1.5 (1.1–2.0) |
| | | | $p = 0.004$ | $p = 0.006$ |
| Alcohol intake in 1986 (%)[d] | | | | |
| Never | 56.9 | 52.8 | 1 | 1 |
| <4 g/day | 23.6 | 22.4 | 1.0 (0.9–1.2) | 1.0 (0.8–1.2) |
| ≥4 g/day | 19.5 | 24.8 | 1.4 (1.1–1.6) | 1.1 (0.9–1.4) |
| | | | $p = 0.0007$ | $p = 0.3$ |
| Regular physical activity in 1986 (%) | | | | |
| No | 57.9 | 63.7 | 1 | 1 |
| Yes | 42.1 | 36.3 | 0.8 (0.7–0.9) | 0.8 (0.7–1.0) |
| History of HT use up to 2004 (%) | | | | |
| Never | 56.1 | 51.7 | 1 | 1 |
| Ever | 43.9 | 48.3 | 1.2 (1.0–1.4) | 1.19 (1.0–1.4) |
| Diabetes up to 2004 (%) | | | | |
| Never | 84.2 | 80.7 | 1 | 1 |
| Ever | 15.8 | 19.3 | 1.4 (1.2–1.7) | 1.4 (1.2–1.7) |
| Heart disease up to 2004 (%) | | | | |
| Never | 86.6 | 85.4 | 1 | 1 |
| Ever | 13.4 | 14.6 | 1.2 (1.0–1.4) | 1.1 (1.0–1.3) |
| Hypertension up to 2004 (%) | | | | |
| Never | 57.8 | 54.1 | 1 | 1 |
| Ever | 42.2 | 45.9 | 1.3 (1.07–1.5) | 1.2 (1.1–1.5) |

[a] Mean ± standard deviation

[b]Prevalent odds ratio

[c]Adjusted for age, education, smoking status, pack-years of smoking, alcohol, and BMI

[d]These variables were adjusted for each other in multivariate-adjusted analyses

**Table 2**

Associations between psoriasis and risk of total cancer and cancers of breast, lung, and colon, IWHS/Medicare, 1991–2006

| Incident cancer | Psoriasis | Number of cancers | Person-years | Incidence rate per 1,000, age-adjusted | HR, age-adjusted (95% CI) | HR, multivariate-adjusted[a] (95% CI) |
|---|---|---|---|---|---|---|
| Total | No | 6,381 | 384,037 | 16.5 | 1 | 1 |
| | Yes | 107 | 5,141 | 20.8 | 1.2 (1.0–1.4) | 1.1 (0.9–1.4) |
| Breast[b] | No | 2,037 | 402,199 | 5.1 | 1 | 1 |
| | Yes | 29 | 5,477 | 5.3 | 1.0 (0.7–1.5) | 1.0 (0.7–1.5) |
| Lung | No | 722 | 414,074 | 1.7 | 1 | 1 |
| | Yes | 20 | 5,703 | 3.5 | 1.9 (1.2–3.0) | 1.3 (0.8–2.0) |
| Colon | No | 925 | 411,031 | 2.2 | 1 | 1 |
| | Yes | 22 | 5,637 | 3.9 | 1.6 (1.1–2.5) | 1.6 (1.0–2.4) |

[a] Adjusted for age at the start of follow-up, BMI, education, smoking status, pack-years, physical activity, and history of HT use

[b] Additionally adjusted for number of live births

## Table 3

Multivariate-adjusted hazard ratios (HR) of total cancer and cancers of breast, lung, and colon, according to psoriasis severity, 1991–2006

| Cancer | No psoriasis | | Mild psoriasis | | Severe psoriasis | | p trend[b] |
|---|---|---|---|---|---|---|---|
| | Number of cancers | HR | Number of cancers | HR (95% CI) | Number of cancers | HR (95% CI) | |
| Total | 6,381 | 1 | 85 | 1.1 (0.9–1.4) | 22 | 1.2 (0.8–1.8) | 0.3 |
| Breast[a] | 2,037 | 1 | 24 | 1.4 (0.8–2.2) | 5 | 1.0 (0.4–2.7) | 0.4 |
| Lung | 722 | 1 | 16 | 1.1 (0.7–1.6) | 4 | 1.0 (0.4–2.3) | 0.9 |
| Colon | 925 | 1 | 17 | 1.5 (0.9–2.4) | 5 | 1.9 (0.8–4.7) | 0.03 |

Adjusted for age at the start of follow-up, BMI, education, smoking status, pack-years, physical activity, and history of HT use

[a] Additionally adjusted for number of live births

[b] Test for trend across psoriasis groups was calculated by putting a psoriasis severity variable (0—no psoriasis, 1—mild, 2—severe psoriasis) as a continuous variable into the model