

The Burden of Skin Diseases 2004

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Association

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Foreword

At any given time, one out of every three people in the United States suffers from a skin disease.

Skin disease was cited recently as one of the top 15 groups of medical conditions for which prevalence and health care spending increased the most between 1987 and 2000.¹ Even so, a national data profile on skin disease has not been updated since 1979. As identified in this study, conditions such as herpes simplex and zoster, sun damage, hair and nail disorders, contact dermatitis and human papillomavirus and warts are highly prevalent in the U.S.

The burden of skin disease extends beyond the financial toll, estimated at more than \$39.0 billion per year in medical services and lost productivity. There are more than 3,000 identified varieties of skin disease that can cause symptoms ranging from simple burning and itch, to severe emotional and social effects, to physical disfigurement or death.

The American Academy of Dermatology Association and the Society for Investigative Dermatology recognized the need to compile and analyze available data. This study was commissioned to estimate the prevalence, economic burden and quality of life impact of a defined group of skin diseases.

It is the hope of our organizations that this report will increase your awareness of the true burden of skin disease.

David R. Bickers, M.D., Chairman
Burden of Skin Disease Technical Panel

¹ Thorpe KE, Florence CS, Joski P. Which medical conditions account for the rise in health spending? Health Affairs 2004;22(2):W4-437-45.

Executive Summary

Skin diseases have a broad and burdensome impact on the health and well-being of Americans, and account for substantial health care costs to the nation. Skin disease is one of the top 15 groups of medical conditions for which prevalence and health care spending grew the most between 1987 and 2000, exceeding spending rate increases for diabetes, cerebrovascular disease, and cancer.² The purpose of this study, sponsored by the Society for Investigative Dermatology (SID) and the American Academy of Dermatology Association (AADA), was to estimate the prevalence, annual economic burden, and quality of life implications of a major group of skin diseases.

Some 3,000 varieties of skin disease, including many rare ones, have been identified in the medical literature. Epidemiological and other data sets track some, but not all, of the most prevalent ones, including certain groups of related diseases. The 21 disease categories selected for this study were chosen by an expert panel of dermatologists to represent the national impact of skin disease based on prevalence, severity, and other factors. As the purpose of this study is to estimate the national burden of skin disease rather than of diseases that are treated primarily by dermatologists, this report covers certain diseases that are treated primarily by other specialists, such as skin ulcers and wounds, lupus erythematosus, and cutaneous T-cell lymphoma. Inclusion or exclusion of a particular condition is not necessarily indicative of its clinical or economic importance relative to other conditions. Some disease categories included in this study comprise multiple skin diseases.

Based on estimates for prevalence, direct costs, indirect costs associated with lost productivity, and intangible costs associated with diminished quality of life, the burdens of the 21 skin disease categories selected for this study are summarized in **Figure E.1**. The most prevalent of these conditions in 2004 were: herpes simplex (based on seroprevalence), effects of sun exposure, contact dermatitis, hair and nail disorders, and human papillomavirus. To capture the wide range of skin disease, this study also included diseases with low prevalence, but often with severe burden on the individuals with those conditions. While such conditions as cutaneous T-cell lymphoma, immuno-bullous diseases, and lupus erythematosus are among the less prevalent skin diseases, they often have debilitating personal effects on health and quality of life.

The total estimated annual cost of the 21 skin disease categories analyzed in this study is \$39.0 billion in 2004 dollars, including the value of medical costs and lost productivity. The total direct and indirect costs for each of these categories range from \$157 million for cutaneous drug eruptions to \$12 billion for skin ulcers and wounds. Among the 21 disease categories, the five most economically burdensome, based on direct and indirect costs, are skin ulcers and wounds, melanoma, acne, nonmelanoma skin cancer, and contact dermatitis, comprising a total of \$22.8 billion.

² Thorpe KE, Florence CS, Joski P. Which medical conditions account for the rise in health spending? *Health Affairs* 2004;22(2):W4-437-45.

Figure E.1. Prevalence and Direct, Indirect and Intangible Costs of Selected Skin Diseases, U.S. (2004)

| Disease | Prevalence† (millions) | Direct Cost§ (millions) | Indirect Cost Due to Lost Productivity (millions) | Total Direct and Indirect Cost** (millions) | Intangible Cost due to QoL Impact (millions) |
|-----------------------------|---------------------------|----------------------------|------------------------------------------------------|------------------------------------------------|-------------------------------------------------|
| Actinic keratosis | 58.08 | \$1,166 | \$286 | \$1,452 | \$5,838 |
| Melanoma | 0.72 | \$291 | \$2,852 | \$3,143 | \$367 |
| Cutaneous T-cell lymphoma | 0.02 | \$44 | \$242 | \$286 | \$9 |
| Nonmelanoma skin cancer | 1.23 | \$1,451 | \$961 | \$2,412 | \$125 |
| Contact dermatitis | 72.29 | \$1,625 | \$566 | \$2,191 | \$1,946 |
| Atopic dermatitis | 15.17 | \$1,009 | \$619 | \$1,628 | \$2,585 |
| Seborrheic dermatitis | 5.87 | \$179 | \$51 | \$230 | \$1,215 |
| Herpes simplex and zoster | 188.61 | \$1,704 | \$261 | \$1,965 | \$8 |
| Human papillomavirus | 58.49 | \$939 | \$214 | \$1,153 | \$2,505 |
| Cutaneous fungal infections | 29.37 | \$1,671 | \$282 | \$1,953 | \$453 |
| Vitiligo | 1.15 | \$175 | \$55 | \$230 | \$63 |
| Acne | 50.18 | \$2,486 | \$619 | \$3,105 | \$11,969 |
| Rosacea | 14.68 | \$385 | \$80 | \$465 | \$1,560 |
| Benign neoplasms | 29.37 | \$1,402 | \$281 | \$1,683 | \$1,564 |
| Hair and nail disorders | 70.46 | \$780 | \$175 | \$955 | \$17,398 |
| Lupus erythematosus | 0.36 | \$347 | \$201 | \$548 | \$36 |
| Immuno-bullous diseases | 0.14 | \$197 | \$65 | \$262 | \$14 |
| Psoriasis | 3.14 | \$1,224 | \$114 | \$1,338 | \$2,306 |
| Skin ulcers and wounds | 4.78 | \$9,712 | \$2,239 | \$11,951 | \$968 |
| Effects of sun exposure | 123.15 | \$434 | \$33 | \$467 | \$993 |
| Cutaneous drug eruptions | 2.64 | \$116 | \$41 | \$157 | \$12 |
| OTC costs, other‡ | - | \$1,418 | - | \$1,418 | - |
| Total* | - | \$28,755 | \$10,237 | \$38,992 | \$51,934 |

† Prevalence estimates are drawn from multiple data sources, all of which are adjusted to 2004 equivalents.

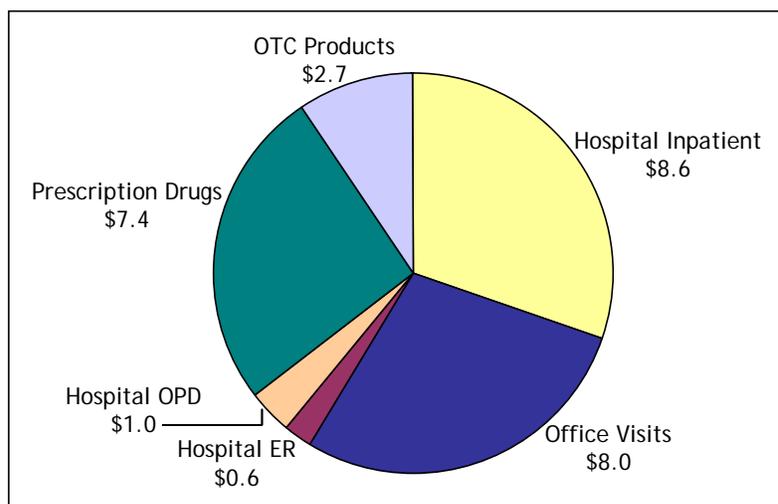
§ Estimates based on 2002-2003 National Ambulatory Medical Care Survey, 2002-2003 National Hospital Ambulatory Medical Care Survey, 2001 Medicare Standard Analytic File, 2003 Scott-Levin Source Prescription Audit, and AC Nielsen OTC Data.

‡ OTC costs not attributable to a particular condition, with the exception of acne, psoriasis, jock itch, sunburn, hair growth products; see Chapter 9 for details.

* Inflated to 2004 dollars using Medical CPI.

** Indirect cost estimates include only lost days of work due to consumption of health care. Estimates based on other studies in the literature are noted throughout this report.

Figure E.2. Direct Cost of Skin Diseases by Cost Component, U.S.
(\$ billions, 2004)



**This graph does not include the approximately \$425 million spent on nursing home care for skin ulcers and wounds.*

The direct medical costs for each of the 21 skin disease categories are broken down by expenditures on prescription drugs, over-the-counter (OTC) products, and services provided in physician offices, hospital outpatient departments, emergency rooms and inpatient facilities (**Figure E.2**). Of the nearly \$28.8 billion spent on direct medical costs (physician visits, medications, etc.), \$8.6 billion was spent on inpatient care, \$9.6 billion on ambulatory care, and \$10.1 billion on prescription and OTC products.

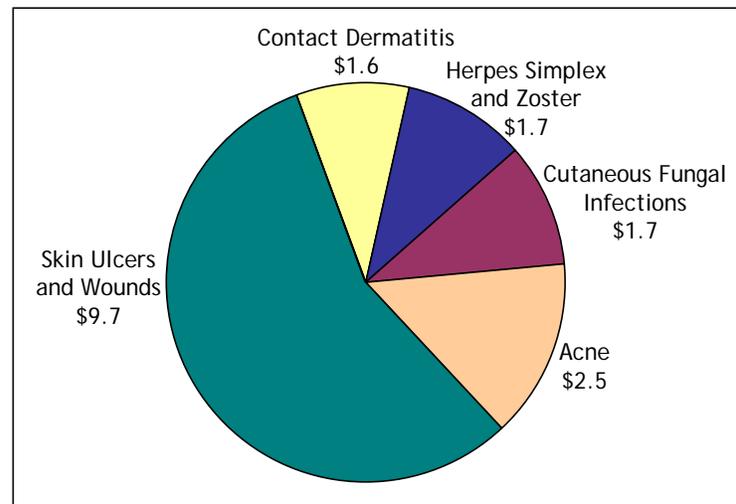
Site of service costs are not proportionately related to utilization. Although total hospital inpatient costs and physician office costs are of similar magnitude, the great majority of visits (75.6 million) were made to physician offices. Inpatient hospital stays with a primary diagnosis of one of the skin conditions of interest were relatively few (439,600) and driven largely by a small set of diseases, particularly skin ulcers and wounds, herpes simplex and zoster, and nonmelanoma skin cancer. The disproportionate relationship between visits and costs associated with inpatient versus outpatient settings of care is an indication of the steeply higher costs associated with advancing severity for certain of these conditions. These values also highlight the potential economic impact of shifting from inpatient to outpatient care for preventive and ambulatory services for many dermatological conditions.

In general, the relative distribution of these costs across the disease categories included in this study is highly variable, though the two largest categories of direct medical costs across the majority of conditions are outpatient health services and prescription drug costs. As noted above, the most frequent site of service by far is the physician office for outpatient care. Other important variations in direct medical costs for these conditions include the level and intensity of prescription drug use for these conditions. For conditions such as acne, herpes simplex and zoster, rosacea, and cutaneous fungal infections, the cost of prescription drugs represents a large portion of the total direct medical costs. In certain cases, a small number of drugs account for a large proportion of the prescription drug spending for a particular disease (e.g., herpes simplex, cutaneous fungal infections, and human papillomavirus).

OTC products are used heavily in the treatment of many skin diseases. However, because of the manner in which these costs are tracked (typically by commercial product category but not by disease-specific diagnostic or procedural codes), it was not possible to allocate most OTC costs to specific diseases included in this report, with a few exceptions such as acne, psoriasis and sun damage. Chapter 9 highlights the distribution of OTC cost categories that can be attributed reasonably in the aggregate to the 21 disease categories considered in this report. Though the OTC costs were found to represent only about 9% of the total direct costs associated with skin diseases, these costs may be under-represented overall due to data limitations and constitute a sizable portion of expenditures for certain skin diseases (e.g., dermatitis, vitiligo, and cutaneous fungal infections). For example, OTC products (such as special purpose creams or tar-based shampoos) account for approximately 78% of direct costs for sun exposure care.

Considering direct medical costs only, the five most costly categories of skin disease are skin ulcers and wounds, acne, herpes simplex and zoster, cutaneous fungal infections, and contact dermatitis, for a total of \$17.2 billion, as shown in **Figure E.3**. As a group, these account for 60% of total direct medical costs for the 21 disease categories.

Figure E.3. Top 5 Skin Diseases by Direct Medical Cost, U.S.
(\$ billions, 2004)

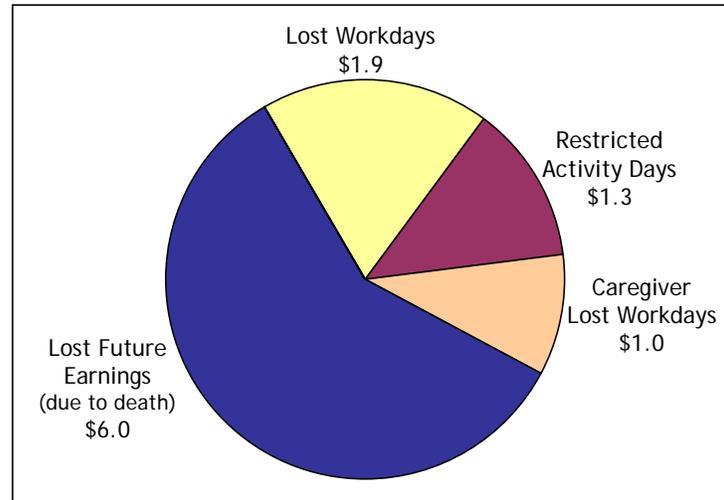


Skin conditions affect productivity, as they can require patient and caregiver time away from work or leisure activities in pursuit of medical attention. Many of these conditions limit daily activities. In cases where a skin condition results in a fatality, the value of the individual's foregone future earnings due to premature death must also be considered.

The total indirect cost associated with lost productivity for these conditions is \$10.2 billion. Since not everyone participates in the workforce, valuation of lost productivity accounted for such factors as age (i.e., likelihood of being in the workforce) and probability of a caregiver's involvement in seeking medical care for these conditions. As shown in **Figure E.4**, the largest component of indirect costs is lost future earnings due to premature death, reflecting 59% of total indirect costs. While relatively few skin conditions are fatal, even low mortality rates can result in significant productivity losses, especially if the condition takes the life of a younger person. Individual and caregiver lost workdays accounted for \$2.9

billion or 29% of these indirect costs, with restricted activity days comprising a smaller proportion of total indirect costs.

Figure E.4. Lost Productivity Attributable to Skin Conditions, U.S.
(\$ billions, 2004)



Intangible costs associated with impact on quality of life were estimated using “willingness-to-pay” for relief of the symptoms associated with these conditions. This approach for valuation of quality of life deficits is used in health economic evaluations to derive the amount of money that individuals would be willing to pay in order to achieve relief from their symptoms.³ While some economists consider intangible costs to be a form of indirect costs, they are considered independently in this study. (To the extent that these conditions diminish ability to work or enjoy leisure activities, they are reflected in indirect costs.) The willingness-to-pay approach assigns an economic value to the intrinsic effect that these conditions have on health-related quality of life.⁴ Since many of these conditions are chronic, physically noticeable, and often difficult to treat, their effects on quality of life may be more pronounced than those of other disease types. For example, patients with atopic dermatitis, acne, or psoriasis have reported greater detrimental impact on quality of life than patients with such conditions as asthma, angina, and hypertension.⁵

Patients with skin conditions report experiencing deficits in quality of life that can exceed many non-skin related conditions. Major types of symptoms include debilitating itching, mobility impairments, and severe psychosocial effects. Skin conditions may interfere with activities of daily living by, for example, restricting motion, and are also often psychologically debilitating because of their physical discomfort, outward manifestations, and impact on patient confidence and sense of well being.

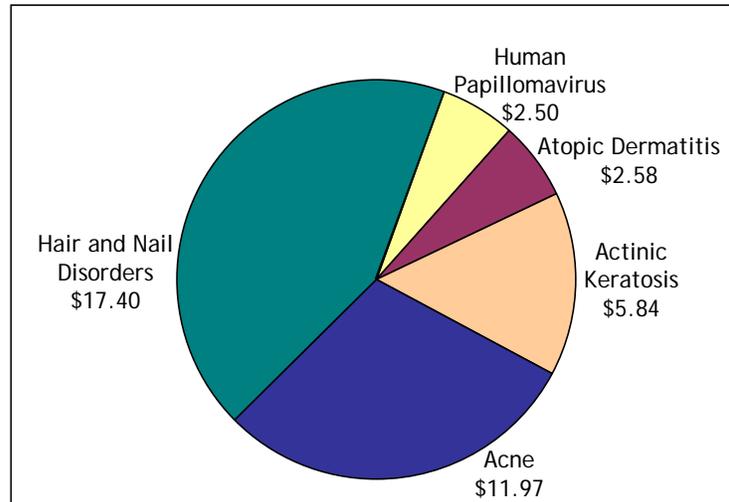
³ Drummond MP, O’Brien B, Stoddard GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. New York: Oxford University Press; 2000.

⁴ Gold MR, Siegel JE, Russel LB, Weinstein MC. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.

⁵ Parks L, Balkrishnan R, Hamel-Gariepy L, Feldman SR. The importance of skin disease as assessed by “willingness-to-pay”. *J Cutan Med Surg* 2003 Sep-Oct;7(5):369-71.

The total estimated intangible cost associated with these conditions is \$51.9 billion. Five disease areas accounted for 76% of the total willingness-to-pay for symptom relief: hair and nail disorders, acne, actinic keratosis, atopic dermatitis, and human papillomavirus and warts (**Figure E.5**). Thus, affected individuals would be willing to pay a total of \$40.3 billion for symptom relief, indicating the substantial effects that these conditions have on quality of life that are not captured in estimates of direct medical costs or lost productivity.

Figure E.5. Top Five Conditions by Willingness-to-pay for Symptom Relief, U.S. (\$ billions, 2004)



Some individuals are disproportionately affected by certain of these 21 categories of skin diseases, including those who do not have health insurance coverage or the means to access health care services due to socioeconomic status or other circumstances. Also, health care for some of these 21 disease categories does not meet conventional interpretations of medical necessity criteria used by many health care payers, preventing patients from receiving coverage for associated care. While some of these diseases are widely recognized as having “only” cosmetic effects (e.g., vitiligo, certain hair disorders) and are rarely fatal, they have high indirect and/or quality of life burdens for many people.

There are sizeable gaps in nationally representative datasets for approximating the prevalence of many of the conditions reviewed here, presenting a challenge to deriving national estimates. In these cases, reliance on methodologically sound, peer-reviewed studies was necessary.

The significant health and economic burden of skin disease in the U.S. and the considerable data gaps associated with many of these diseases call attention to the need for research into their etiology, epidemiology, prevention and treatment. National Institutes of Health (NIH) funding for research on skin diseases is provided by multiple Institutes (including the National Cancer Institute and National Institute of Allergy and Infectious Diseases), though the primary center is the National Institute of Arthritis and Musculoskeletal and Skin Diseases, which allocated \$78.9 million for skin disease research in 2005.⁶ The National Cancer Institute committed more than \$90 million for melanoma research and \$2.8 million

⁶ Research expenditures provided by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. National Institutes of Health 2005.

for certain other skin cancers under the Specialized Programs of Research Excellence (SPORE).⁷ Though other research on skin diseases is funded by these and other Institutes, these figures account for the majority of federal spending on skin disease research. This level of funding is considerably lower than funding for other similarly economically burdensome diseases. For example, NIH funding in 2005 is estimated to be \$396 million for kidney disease and \$383 million for arthritis, about twice the amount allocated for research on skin diseases.⁸

Disparities in R&D funding relative to burden of disease have been well-documented.^{9,10} This report extends previous studies by quantifying cost impacts of hospitalization and outpatient care, pharmaceuticals, OTC expenditures (where available), losses of productivity, and diminished quality of life. This not only highlights the relative health and economic burden and impacts of skin disease in the U.S., but accounts for the considerable magnitude of quality of life deficits associated with many of these diseases. Such indirect cost and quality of life impacts may not be considered sufficiently in setting R&D spending priorities for human health research.

The considerable national burden of skin diseases documented in this report – including population and personal clinical burden and costs – cannot go unrecognized in policy making for R&D investment, health care delivery and payment, and setting of national health care priorities. As health care is increasingly subject to cost containment and demand for improved health and quality of life, allocation of funding should better reflect national impacts of disease on health status and costs. As one of the most costly and rapidly expanding medical conditions in the U.S., the relative burden associated with skin diseases is a growing concern relevant to the health and economic well-being of the nation.^{11,12}

⁷ Specialized Programs of Research Excellence, Fiscal Year 2003. NCI Factbook. National Institutes of Health. Accessed March 15, 2005: <http://www3.cancer.gov/admin/fmb/03Factbk.pdf>

⁸ Estimates for funding for various diseases, condition, research areas. National Institutes of Health. Accessed February 9, 2005: <http://www.nih.gov/news/fundingresearchareas.htm>.

⁹ Gross CP, Anderson GF, Rowe NR. The relation between funding by the National Institutes of Health and the burden of disease. *N Engl J Med* 1999;340(24):1881-87.

¹⁰ Scientific opportunities and public needs: improving priority setting and public input at the National Institutes of Health. Washington, DC: The National Institute of Medicine 1998.

¹¹ Cohen JW, Krauss NA. Spending and service use among people with the fifteen most costly medical conditions, 1997. *Health Affairs* 2003;22(2):129-138.

¹² Thorpe 2004.

Chapter 1: Introduction

Skin conditions are among the most common health problems of Americans, collectively exceeding the prevalence of conditions such as obesity, hypertension and cancer. Estimates suggest that at any one time, one-third of the U.S. population is experiencing at least one active skin condition.¹³ The considerable costs of skin diseases are generated by physician visits, hospital care, prescription drugs, and over-the-counter products necessary for treating or managing these conditions, as well as indirect costs due to productivity losses. While most skin conditions are not life threatening, many pose significant clinical burdens to populations and individuals as well as deficits to quality of life. The Society for Investigative Dermatology (SID) and the American Academy of Dermatology Association (AADA) commissioned this study to evaluate the clinical, economic, and quality of life impacts of 21 leading categories of skin diseases in the U.S.

Some 3,000 varieties of skin disease have been identified in the clinical literature, many of which are rare, and epidemiological and other data sets account for a subset of the most prevalent ones, including certain groups of related diseases. Therefore, the diseases selected for this study were chosen by an expert panel of dermatologists to reflect broadly the national impact of skin disease based on such factors as severity and prevalence. As the purpose of this study is to estimate the national burden of skin disease rather than of diseases that are treated primarily by dermatologists, this report covers certain diseases that are treated primarily by other specialists, such as skin ulcers and wounds, lupus erythematosus, and cutaneous T-cell lymphoma. Inclusion or exclusion of a particular condition is not necessarily indicative of its clinical or economic importance relative to other conditions. Some disease categories included in this study, such as cutaneous fungal infections, hair and nail disorders, and immuno-bullous diseases, comprise multiple skin diseases.

Previous studies of the economic burden associated with skin conditions have been conducted with varying methods and results. A study reported by Dehkharghani et al. in 2003 estimated the total annual cost of skin diseases at \$35.9 billion in 1997 U.S. dollars, with \$34.3 billion attributable to direct costs, including hospital and ambulatory visit costs, prescription drugs and OTC products.¹⁴ That study included a much broader spectrum of skin diseases and used different methodological assumptions than the present study. Assumptions related to (a) the relationship between utilization of health services and associated costs and (b) selection of specific diagnostic and procedural codes to characterize utilization account for the primary differences in cost estimates for ambulatory, procedural, prescription drug, OTC and other costs associated with skin diseases. For example, in calculating ambulatory care costs, Dehkharghani et al. assumed that the average cost of an ambulatory dermatological visit was equivalent to the average cost of all ambulatory visits, irrespective of the purpose of the visit or the mix of medical, surgical, laboratory, or other

¹³ Johnson ML. Defining the burden of skin disease in the United States--a historical perspective. *J Investig Dermatol Symp Proc* 2004;9(2):108-10.

¹⁴ Dehkharghani S. The economic burden of skin diseases in the United States. *J Am Acad Dermatol* 2003;48(4):592-9.

procedures used in the ambulatory setting. As such, the differences in direct costs estimated by Dehkharghani et al. and those presented here are largely attributable to methodological differences in selecting conditions of interest and assigning costs associated with these conditions. Our methods are described in Chapter 2.

Three types of sources were used to describe the impact of skin conditions. The first source was a detailed review of the literature on the costs, epidemiology and quality of life associated with each of the 21 disease categories. The second source was a set of nationally representative databases generated by the federal government, including the:

- National Health Interview Survey (NHIS)
- National Hospital Discharge Survey (NHDS)
- National Hospital Ambulatory Medical Care Survey (NHAMCS)
- National Ambulatory Medical Care Survey (NAMCS)
- National Health and Nutrition Examination Survey (NHANES)
- Medicare Standard Analytic Files
- Surveillance, Epidemiology and End Results (SEER)
- National Vital Statistics Reports (NVSS)

The third source type, proprietary data sources, included the Scott Levin Source Prescription Audit (SPA) to estimate prescription drug costs and AC Nielson data to capture OTC product costs.

There were several types of limitations to developing estimates of the cost of skin diseases for these 21 categories. Among these were the lack of prior studies in the literature, ambiguous or divergent prevalence estimates, and lack of sufficiently detailed data characterizing certain diseases and costs in the nationally representative datasets. In particular, indirect cost estimates for each condition may be understated, as data were often limited for individual disease categories. Also, as opposed to other direct costs, most OTC costs are not tracked by relevant diagnostic or procedural codes, which prevents their allocation to the various disease categories considered. Therefore, we report only OTC product costs that were clearly associated with the 21 disease categories included in our analysis. For example, the costs of such products as baby powder and petroleum jelly are not included here, though products such as these are frequently used to treat common skin conditions. Due to these considerations, the results of this study may understate the actual economic burden of skin conditions in the U.S.

This report is organized into nine chapters. The chapter on methods describes the study approach and reviews the techniques, data sources, and assumptions used. The subsequent chapters address several groupings of the 21 disease categories, including skin cancer and precancerous conditions, dermatitis, microbial skin conditions, chronic conditions of skin complexion, skin conditions due to immune system response and exogenous skin conditions. A separate chapter on OTC costs is presented.

Chapter 2: Methods

This chapter describes methods used to derive estimates of the prevalence and cost of skin diseases. In brief, this study incorporated data from nationally representative data sources on disease prevalence, mortality, utilization of health services, and health expenditures, as well as information from the peer-reviewed medical literature. Corresponding ICD-9 codes for the 21 disease categories were identified and used to guide database searches. Systematic literature searches complemented the database searches to validate findings and provide estimates where prevalence or cost data were unreliable (e.g., due to small sample sizes) or unavailable. Diseases and supporting data were classified into clinically meaningful categories to enhance analysis and interpretation of results.

Selection of Conditions for Inclusion

Skin diseases are extraordinarily diverse in clinical presentation, severity, and epidemiology. These diseases are caused or exacerbated by such factors as genetic predisposition, environment, stress, and presence of comorbid conditions. For this study, diseases were selected based on their contribution to health and economic burden, as determined by the medical literature and expert input from dermatologists assigned by SID and AADA. The conditions reflected here range from those that are life-altering, such as psoriasis and rosacea to those that are also life-threatening, such as melanoma and cutaneous lymphoma.

Based on the 21 disease categories selected, ICD-9 codes were assigned and reviewed by the panel to ensure that the analysis captured the varied and multiple conditions within certain disease categories. Table 2.1 lists alphabetically the diseases included in this study, along with corresponding ICD-9 codes used for database searches.

**Table 2.1. Skin Condition Categories
by International Classification of Diseases (ICD-9) Diagnostic Codes**

| Disease | ICD-9 Codes |
|----------------------------------|---------------------------------------------------------------------------------------|
| Acne (cystic and vulgaris) | 706.1 |
| Actinic keratosis | 702.0, 702.1 |
| Atopic dermatitis | 691.8 |
| Benign neoplasms/keloid | 216, 221.1, 221.2, 222.0, 222.1, 222.4, 701.4 |
| Immuno-bullous diseases | 277.1, 694.0-694.5, 694.60, 694.61, 694.8, 694.9, 695.1, 705.81, 757.39, 919.2, 919.3 |
| Contact dermatitis | 692.0- 692.6, 692.81, 692.83, 692.89, 692.9 |
| Cutaneous fungal infections | 110, 111, 112.3, 117.1, 117.2, 117.4 |
| Cutaneous lymphoma | 202.1, 202.2 |
| Drug eruptions | 693.0, 693.1, 693.8, 693.9 |
| Hair and nail disorders | 703.0, 703.8, 703.9, 704 |
| Herpes simplex and herpes zoster | 053.0-053.2, 053.7-053.9, 054.0-054.9 |
| Human papillomavirus/warts | 078.1, 079.4 |
| Lupus erythematosus | 373.34, 695.4, 710.0 |

| Disease | ICD-9 Codes |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Melanoma | 172 |
| Psoriasis | 696.1 |
| Seborrheic dermatitis | 690.1 |
| Skin ulcers and wounds | 250.7, 250.8, 454.0, 454.2, 707.0, 707.1, 707.8, 707.9, 896.0-896.3, 897.0-897.7, 879.8, 879.9, 941, 942, 943, 944, 945, 946, 948, 949, 991.0-991.3 |
| Non melanoma skin cancer | 173.0-173.8 184.1-184.4, 187.1-187.3, 232.0-232.9 |
| Vitiligo | 374.53, 709.0 |
| Damage from solar radiation | 692.70-692.77, 692.79 |

Resource Utilization and Cost Analysis

To develop reliable estimates of health care resource utilization and corresponding costs from available databases, we identified cost components representing various relevant health care services and resources. Utilization was measured for each major type of service, including physician care, inpatient hospital care, outpatient hospital care, emergency (urgent) care, and pharmaceutical therapy. Table 2.2 lists the health care resources and corresponding cost components included in this study.

Table 2.2. Utilization and Cost Variables Considered

| Service/Resources | Cost Components |
|----------------------------|--------------------------------------------------------------------------------------------------------------|
| Physician office visits | Physician costs |
| Inpatient hospitalization | Facility costs associated with inpatient stays, physician costs for inpatient physician services |
| Outpatient hospitalization | Facility costs associated with outpatient visits, physician costs for hospital outpatient physician services |
| Emergency care | Emergency room costs, physician costs for emergency room services |
| Pharmaceutical therapy | Pharmaceutical costs as determined in the Source Prescription Audit |
| OTC products | Drugs and topical therapy purchased without a doctor's prescription |
| Work loss | Indirect costs or valuation of work loss secondary to receiving health care |
| Lost future earnings | Estimated lost future earnings due to premature death |

Literature Review

We conducted an extensive literature search to supplement epidemiologic and cost data derived from the nationally representative and proprietary databases for these 21 disease categories. Sources for the literature search primarily included, but were not limited to, PubMed/MEDLINE and the Cochrane Databases using combinations of MeSH (Medical Subject Heading) terms and text words. The MeSH terms used to direct the bibliographic searches included names of particular diseases (e.g., melanoma, rosacea) used alone and in combination with terms (MeSH and text words) for such concepts as prevalence, epidemiology, costs and cost of illness, productivity/work loss and quality of life. Citations were limited to those published within the last 10 years and to articles published in English. In addition to the peer-reviewed literature, other authoritative sources were searched, including clinical practice guidelines from the National Guideline Clearinghouse and

systematic reviews available from the Agency for Healthcare Research and Quality (AHRQ), publications by government agencies such as the National Institute of Allergy and Infectious Diseases (NIAID), and medical professional or disease-specific organizations such as the American Cancer Society and the National Psoriasis Foundation. When applicable, references cited in these publications were also cited and used as resources. In addition, we consulted the SID and AADA advisory panel to the study to identify any seminal studies reporting well-founded estimates of disease prevalence and/or cost.

In total, more than 200 articles were identified as containing information on the epidemiology, resource utilization, or costs associated with the 21 disease categories under review. We reviewed each article for reliability of content and relevance to current treatment patterns (if an economic study). Studies with inadequate sample sizes or obviously flawed study designs were not included as data sources or used to validate study findings.

The literature was the primary source for disease prevalence when the study diseases were clearly over- or under-represented in the national databases. For example, a disease was under-represented when the sample size for a particular population in a national database was too small to reliably estimate prevalence or costs. Alternatively, a disease was over-represented when patient data for that disease was aggregated with similar diseases. For the 21 disease categories studied, the majority (acne, actinic keratosis, nonmelanoma skin cancer, benign neoplasms, immuno-bullous diseases, cutaneous fungal infections, cutaneous lymphoma, cutaneous drug eruptions, hair and nail disorders, herpes zoster, human papillomavirus, psoriasis, rosacea, and vitiligo) were considered to be under-represented in national datasets. Conversely, atopic dermatitis, contact dermatitis, and seborrheic dermatitis were considered to be over-represented because they are frequently consolidated into one category. For these diseases, well-designed peer-reviewed articles served as the main data source for descriptive epidemiology. Two other conditions, sunburn and herpes simplex, were found to be well-described in population-based studies found in the literature. Since the methods of these studies were found to be more rigorous than those of the nationally-representative datasets, (i.e., included provisions to reduce recall bias or limit self-reporting of conditions) for these two conditions, epidemiological estimates also were drawn from these sources.

Databases

Due to the varied nature of the selected diseases, this study used data from several nationally representative databases, both publicly available and proprietary, to develop estimates of the prevalence, health care utilization, and costs associated with these conditions. The literature was used to validate or supplement findings from the database analyses.

Initial sources for estimating prevalence and utilization were nationally representative datasets, including the National Health Interview Survey (NHIS), the National Ambulatory Medical Care Survey (NAMCS), the National Hospital Ambulatory Medical Care Survey (NHAMCS), and the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute (NCI). For any given health services utilization estimate, we averaged the utilization from the 2002 and 2003 datasets to minimize any residual effects resulting from small sample sizes. Where data from these sources appeared insufficient to

derive reliable estimates, we consulted the literature as described above. Among the factors contributing to low representation in these datasets are the low rate of hospitalization for many skin diseases and the fact that certain diseases (e.g., psoriasis and acne) are often self-treated using OTC products. As noted above, the sampling methodologies for some national datasets may be too limited to capture sufficient data to characterize these diseases. An example of an important limitation in desirable data is that the most recent dermatology-specific component of the NHIS is from 1996, presenting a challenge to estimating current disease prevalence.

Databases produced by the National Center for Health Statistics (NCHS), one of the Centers for Diseases Control and Prevention (CDC), were the primary source for disease prevalence and health services utilization data. Since these databases do not contain cost information, other datasets, including the Medicare Standard Analytic Files, were used to assign economic values to the health resources tracked by the NCHS databases. The following describes the capabilities and limitations of each of the databases used in this study.

1996 National Health Interview Survey (NHIS)

Administered by the NCHS, CDC, the NHIS is an annual nationwide survey of civilian households with a sample based on interviews of approximately 100,000 persons from 40,000 households. Survey data are drawn from face-to-face interviews of responsible family members residing in the household. Proxy responses are accepted for family members who are not at home and are required for all children and for all family members who are physically or mentally incapable of responding for themselves. Illnesses are coded using a slight modification of the ninth revision of the *International Classification of Diseases*. According to the NCHS, 1996 was the last year that the NHIS included questions pertaining to most dermatological conditions. Even so, the survey frequently did not ask questions adequate to support specific prevalence estimates for the majority of diseases. In cases where the data allowed, we stratified the epidemiological data by age and sex. In many cases, the literature or other sources were used to derive prevalence estimates.

The primary shortcomings of NHIS are that the data are considerably older than other data sources used in this study (mainly 2002) and the disease occurrences are self-reported. Although a considerable effort is made to ensure accurate reporting, information from both proxy and self-respondents may be under-reported because the respondent is unaware of relevant information, has forgotten it, or does not wish to reveal it to an interviewer. As such, the self-reported nature of NHIS likely results in underestimates of prevalence.

Although the NHIS sample size of 102,000 persons is sufficient for many epidemiological purposes, it is insufficient to capture useful levels of data on many of the skin conditions evaluated in this study. Therefore, the use of this database was limited to diseases in which the unweighted cell count (i.e., the unweighted number of reports of a given disease) was ≥ 30 . As noted above, self-reporting also is likely to introduce error in disease classification, as coders of survey data classified each response to a modified version of the ICD-9-CM codes and subsequently grouped these codes into larger classifications (“condition recodes”). After review of the NHIS, it was determined that prevalence estimates for 18 of the

21 diseases could not be obtained from this dataset due to these limitations. In cases where data from the NHIS sample were not sufficiently detailed or of an acceptable sample size, the literature was used to inform prevalence estimates.

2002-2003 National Hospital Discharge Survey (NHDS)

The National Hospital Discharge Survey (NHDS) is a national survey of inpatient utilization in non-federal short-stay hospitals, children's hospitals, and general hospitals. The database comprises medical records from a nationally representative sample of 270,000 inpatient records drawn from 500 non-federal hospitals. This source was used to capture inpatient hospitalization data, including number of hospitalizations, average length of stay per disease, and the total number of days of care by each disease. As is the case for other NCHS datasets, NHDS does not provide cost or charge information. Therefore, other databases were used to estimate hospital costs.

2002-2003 National Ambulatory Medical Survey (NAMCS)

The National Ambulatory Medical Care Survey (NAMCS), also a NCHS dataset, is a survey of office visits made by ambulatory patients to a nationally representative sample of approximately 1,500 non-federally employed physicians. The settings included in this survey are: free standing private, solo, or group office; free standing clinic; neighborhood health center; privately operated clinic; local government clinic; and health maintenance organization or other prepaid practice. The total number of records (based on visits) is about 23,400. As with the other NCHS datasets, an algorithm prepared by NCHS allows the raw counts to be weighted up to an estimate for the entire nation. The dataset provides information regarding physician office visits for each disease, including number of visits, and demographic data. Visits to physicians in the specialties of anesthesiology, pathology, and radiology are excluded from the survey. An assumption was made that for a given patient, only one visit could occur during any particular day. (This assumption also applies to the NHAMCS dataset, described below).

2002-2003 National Hospital Ambulatory Medical Care Survey (NHAMCS)

Another NCHS source, the National Hospital Ambulatory Medical Care Survey (NHAMCS), includes two relevant files: a hospital emergency department file (ED file) and a hospital outpatient department file (OPD file). Each file has a sample size of 29,400 records (i.e., visits). From these files, data were obtained on the number of ED and OPD visits for each condition.

NHAMCS does not account for certain ambulatory sites of service in which skin diseases are treated. In NHAMCS, the OPD refers to outpatient clinics within a hospital. In this setting, clinics are eligible for NHAMCS if ambulatory medical care is provided under the supervision of a physician, under the auspices of the hospital. Clinics in which only ancillary services are provided, or where physician services are not provided, are not included in the survey. Also, ambulatory surgery centers, whether in hospitals or free-standing centers, are not included in NAMCS or NHAMCS.

2002-2003 Nationwide Inpatient Sample (NIS)

The Nationwide Inpatient Sample (NIS) Release 11 is part of the Healthcare Cost and Utilization Project (HCUP), administered by the Agency for Healthcare Research and Quality (AHRQ). The NIS approximates a 20% sample of U.S. community hospitals, defined by the American Hospital Association as "all non-federal, short-term, general, and other specialty hospitals, excluding hospital units of institutions" for 2002. Included among community hospitals are specialty hospitals, e.g., in obstetrics-gynecology, ear-nose-throat care, short-term rehabilitation, orthopedics, and pediatrics. Excluded are long-term hospitals, psychiatric hospitals, and alcoholism/chemical dependency treatment facilities. NIS Release 11 is based on a stratified probability sample of hospitals, with sampling probabilities proportional to the number of U.S. community hospitals in each stratum. NIS Release 11 is drawn from 35 states and contains information on all inpatient stays from 995 hospitals, totaling about 7.8 million records in 2002. This database was used to estimate the average facility cost per hospital day for each given disease. This value, along with the total days of hospital care per disease (from the 2002 NHDS) was used to calculate the total facility costs associated with hospital inpatient stays. The NIS was also used to estimate the total charges associated with certain physician-administered drugs covered by Medicare such as cancer chemotherapy.

2001 Medicare Standard Analytic Files

The Medicare Standard Analytic Files (SAF) contain all medical claims of 5% of Medicare beneficiaries. These files contain final action, adjustment-resolved claims, and are updated each July with data from the previous calendar service year. Provider numbers and beneficiary claim numbers are encrypted in the 5% files to protect the privacy of individuals. SAF includes the following files: Inpatient (Part A) and Hospital Outpatient, Home Health Agency, Hospice, Skilled Nursing Facility, and Physician/Supplier (Part B). The 2001 Medicare SAF served as the primary source for all procedural utilization and cost data. It was also the source for injectable drugs for nonmelanoma skin cancer, cutaneous T-cell lymphoma, benign neoplasms, and lupus erythematosus, with the costs of injectable drugs for these conditions included in the prescription drug cost estimates.

2004 Scott Levin Source Prescription Audit and the Physician Drug and Diagnosis Audit

The Scott Levin Source Prescription Audit (SPA), drawn from a nationwide sample of pharmacies, served as the source for drug expenditures for each disease. Approximately 35,400 retail pharmacies, accounting for 63% of the entire U.S. retail pharmacy universe, are surveyed on a monthly basis, and 72% of all dispensed prescriptions are captured. This source does not capture the full utilization of drugs administered in physician offices, a common practice for certain skin conditions or drugs acquired via specialty pharmacies. Conditions with a likely substantial proportion of prescription drugs acquired via specialty pharmacy and/or administered in physician offices include actinic keratosis, cutaneous T-cell lymphoma, nonmelanoma skin cancer, benign neoplasms, lupus erythematosus, immunobullous diseases and psoriasis. Disease-specific utilization of drugs, used to determine the proportion of spending that is attributable to a given disease, was measured through the Scott

Levin Physician Drug and Diagnosis Audit. This audit monitors patient visits and associated treatment regimens among approximately 365,000 office-based physicians in 29 specialties across the nine U.S. census regions. It tracks patient drug requests, drug switching, and prescribing volume in the retail pharmacy setting. Diagnosis activity is organized by ICD-9 codes.

2003 AC Nielsen Over-the-Counter Product Sales

OTC product utilization for the categories of acne, solar radiation and some proportion of cutaneous fungal infections (e.g., jock itch remedies), vitiligo (e.g., skin bleaching) and hair disorders (e.g., hair-growth products) were captured using sales statistics from AC Nielsen, a marketing research and information firm. OTC use for other conditions was abstracted from the literature and other sources, as available. The primary shortcoming of this and other sources of OTC data is that it is not possible to link product use to ICD-9 diagnosis and procedure codes, preventing specific assignment to the majority of skin diseases considered in this study.

2001 Surveillance, Epidemiology, and End Results Dataset

The SEER program of NCI compiles data on cancer incidence and mortality as well as patient demographics. SEER includes more than 3 million cases of cancer, collected from 14 population-based cancer registries accounting for 26% of the U.S. population. As the most current data from SEER is for 2001, the prevalence rates by sex and age were applied to the 2004 population to estimate the number of cases of melanoma.

2002 Compressed Mortality File

The CDC WONDER Compressed Mortality File (CMF) was the source for county-level national mortality data. The CMF contains information on the number of deaths, demographics of those who have expired, and the underlying cause of death by ICD-10 codes. The underlying cause of death is defined as “the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury.”¹⁵ The ICD-9 codes selected by the expert panel for the conditions under review in this study were converted to ICD-10 codes for data collection in the CMF.

Measuring Utilization in the Databases

We used the NHDS, NIS, NAMCS, and NHAMCS (ED and OPD files) datasets as the primary sources for estimating utilization figures for inpatient hospital stays, physician office visits, emergency room visits, and hospital outpatient visits, respectively. In addition to stays and visits, the average length of stay and total days of care by disease were obtained from these databases, which were used in calculating indirect costs (as described below). To increase the statistical reliability in the estimates, data from the 2002 and 2003 files were averaged to minimize any residual effect of small sample sizes.

¹⁵ Compressed Mortality File. Atlanta, GA: Centers for Disease Control, 2004. Accessed January 10, 2005. <http://wonder.cdc.gov/mortSQL.html>.

Because the databases used to estimate the resource utilization (e.g., physician office visits, hospital visits, etc.) are based on national probability sample surveys, each visit in the sample is extrapolated, or weighted up, to a nationally representative estimate. These weights, or multipliers, carry a broad range of values due to the purposeful over-sampling of some offices or hospitals in the survey's sampling design. For example, the weight, or multiplier, in the 2003 NHAMCS Emergency Department (ED) dataset ranges from 23 to 15,914. Therefore, when the counts of the "unweighted" visits are small (e.g., less than 30) for a given disease, the potential for under- or over-weighting is greater, and the estimate becomes statistically less reliable.

Several of these specific dermatologic diseases have small counts of unweighted visits for particular visit types (e.g., emergency department visits, inpatient hospitalizations). For this reason, it was decided to analyze two years (2002 and 2003) of each NCHS dataset and calculate the average of the two years' estimates. Across all 21 diseases, this method should, on average, provide more reliable estimates of resource utilization and, therefore, costs.

Estimating Costs

Direct Costs

For each type of service and for each disease, unit costs were applied to the total utilization figures in order to calculate total direct costs. Where data allowed, both utilization and average cost estimates were differentiated by whether the condition appeared as the first-listed (i.e., primary) diagnosis or as one of the second-listed (i.e., secondary, tertiary, etc.) diagnoses. When the condition appeared as a first-listed diagnosis, 80% of the costs of the claim were attributed to this condition. When the condition appeared as a second-listed diagnosis, 20% of the costs of the claim were attributed to the disease. In the relatively few cases when the disease appeared as both a first- and second-listed diagnosis, 100% of the costs of the claim were attributed to the disease.

The primary data source for disease prevalence and utilization of health care services were the NCHS databases. However, these datasets do not include information on costs and charges. Therefore, data on average costs and charges were obtained from other datasets and the literature in order to assign monetary values the health care resources identified in the NCHS databases.

Procedure costs for each site of service were derived from the 2001 Medicare SAF. Costs were adjusted for inflation and extrapolated to 2004 U.S. dollars. Procedure costs were estimated separately for the populations age <65 and \geq 65 years. For Medicare beneficiaries age \geq 65, procedure utilization and costs for each condition were calculated by selecting only those procedures related to that condition at each site of service. Procedural costs for the non-Medicare population were based upon Medicare SAF data and weighted according to age-specific prevalence and utilization estimates for the under-65 population. A modified Delphi technique was also applied as a control for these non-Medicare cost estimates, where dermatological experts were asked to independently assess appropriate procedures for individuals under the age of 65 with each skin condition. Results were then cross-

referenced to utilization assumptions and adjusted as appropriate. Procedure costs were then rolled into cost for the specific site of service (e.g., hospital inpatient, ER).

Inpatient Hospital Costs

The cost of inpatient hospitalizations comprises two components: 1) hospital inpatient facility costs; and 2) physician visits and procedures to inpatients in the hospital. For most conditions, average hospital facility costs were obtained from NIS, and inpatient physician costs were obtained from the Medicare SAF. Inpatient physician visits were assumed to consist of an initial patient consultation for the first day of inpatient care and one follow-up inpatient consult for each subsequent inpatient day, based on average length of stay for each condition.

The 2002-2003 Nationwide Inpatient Sample (NIS) was used to calculate hospital inpatient facility costs. The NIS reports total facility billed charges for each record (i.e., discharge) in the dataset. Hospital charge structures, which include a hospital's markup over costs (including profit and bad debt), tend to overstate the economic resources used in patient care. To account for this, the inpatient facility charges associated with each record (i.e., discharge) in NIS was converted to inpatient facility costs. That is, for each discharge record in the 2002 and 2003 NIS, total charges were multiplied by a hospital-specific ratio of cost-to-charges (RCC) determined by the 2004 Medicare Fee Schedule. For most diseases, this estimated daily cost figure from 2002-2003 Nationwide Inpatient Sample was used to calculate average daily inpatient facility charges, by primary diagnosis, secondary diagnosis, and both. For each disease, these three average daily facility cost figures were adjusted to 2004 dollars and then applied to the appropriate utilization figure (i.e., total number of inpatient days by primary vs. secondary vs. both) calculated from the 2002-2003 NHDS. The sum of these three products represents the total facility costs for that disease in 2004 dollars. As noted above, all cost and utilization data pertaining to the three cancers were acquired from the Medicare SAF.

This methodology may overstate hospital costs for certain diseases. As noted above, for all diseases, 80% of the cost of a hospital claim was attributed to the primary diagnosis, while 20% was applied to a secondary diagnosis. To the extent that a secondary diagnosis actually contributes to 20% of inpatient resource use (e.g., in physician time, prolonged hospitalization), this methodology reflects hospital costs. For dermatological conditions (e.g. actinic keratosis) that are frequently listed as a secondary diagnosis but do not require substantial procedural intervention, this method may actually overstate the hospital costs associated with these conditions.

Outpatient Hospital Costs, Emergency and Physician Office Visit Costs

For the population age ≥ 65 , the 2004 Medicare Fee Schedule (CPT code 99201) was used to determine cost per physician office visit. The 2004 Ambulatory Payment Classification (APC) coding system served as the basis for estimating costs of average facility and physician cost per outpatient hospital visit (CPT code 99201) and average facility and physician cost per emergency room visit (CPT code 99281). These average costs were applied to the utilization figures (i.e., visits by primary diagnosis, secondary diagnosis, and both) from NHAMCS (ED and OPD files) and NAMCS, respectively, to estimate the total costs by setting of care for each disease. The cost per physician office visit for the population

younger than 65 was obtained from a study comparing commercial insurance plans to Medicare.¹⁶

In a manner similar to the derivation of procedure costs for inpatient hospital stays and ER visits, the Medicare SAF was the source for procedure costs in outpatient settings. Procedures for each skin condition were selected based on site of service from the SAF to estimate procedure costs for the Medicare population. For the non-Medicare population, procedure costs were extrapolated based on age-adjusted prevalence rates for each condition, as defined in the inpatient procedural cost section above. These costs were then rolled into outpatient costs at the site of service (e.g., hospital outpatient, physician office).

The Scott-Levin SPA and PDDA were used for information on prescription medications. The total cost of a drug for a particular disease was calculated by applying the diagnosis value factor for the disease to the total drug acquisition cost. Diagnosis value is a share of the use of a given drug for a particular disease weighted by strength and total extended units. OTC costs were obtained from AC Nielsen, where available and reflective of the 21 disease categories evaluated in this study.

Indirect Costs

Indirect costs typically include three categories of time costs: 1) costs related to consumption of medical care, requiring the time of the patient, family, or other caretakers; 2) costs associated with lost or impaired ability to work or enjoy leisure activities due to morbidity; and 3) lost future earning potential due to premature death.¹⁷ This study addressed all three categories of productivity costs.

The nature of the diseases studied resulted in very low unweighted cell counts for work-loss days in NHIS; therefore, for a majority of the diseases, indirect costs were calculated by the valuation of time away from work while seeking medical care. For example, one inpatient hospital day for a person of working age (19-64 years) was assumed to represent one day of missed work for actual time spent in the hospital plus 1.5 days of recovery time. We also assumed that one parent misses work while seeking medical care for a child under the age of 16, the same allotment for time away from work was also assigned to this age category. The corresponding assumptions for ambulatory visits were two hours for physician office visits, four hours for emergency room visits, and four hours for hospital outpatient department visits. These assumed hours were then applied to the total utilization estimates (i.e., days in hospital, ambulatory visits) to estimate days lost from work in those settings.

To value work-loss while seeking medical care, we used U.S. Bureau of Labor Statistics data on average daily wage, stratified by gender and age. To develop a more realistic estimate of the cost of lost productivity, we considered the percent of people participating in the workforce as reported by the Bureau of Labor Statistics. For individuals outside of the workforce, the value of lost productivity was estimated to be half of the corresponding lost productivity of those within the workforce. The lost productivity of children and those age

¹⁶ Kenosha Community Assessment Factbook, 2002. Falls Church,VA: The Lewin Group.

¹⁷ Meunnig P. Designing and Conducting Cost-Effectiveness Analyses in Medicine and Health Care. San Francisco, CA: Jossey-Bass; 2002.

≥ 65 was also valued at half of the corresponding lost productivity of those within the workforce and recorded as a “restricted activity day” as opposed to a “lost workday.”

Separate consideration was given to the lost productivity of caregivers. A caregiver was considered to have lost productive time in seeking care for a child or dependent adult. According to the AARP, 50% of individuals age >50 require assistance with daily activities such as seeing a physician. As with the estimates for individuals with the condition, we stratified the value of caregiver lost productive time according to participation in the workforce.

Lost Future Earnings Due to Premature Death

While few of the skin conditions reviewed in this study are fatal, the value of lost future earnings due to premature death must be considered in calculating the overall burden of skin conditions. To calculate the net present value (NPV) of forgone earnings due to death, the actual number of deaths in 2002 was scaled to the 2004 U.S. population and stratified for age and gender, as reported by the CDC’s Compressed Mortality File (CMF), for each category of skin conditions. Maintained by NCHS, the CMF catalogs the “underlying cause of death,” or the “disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury.”¹⁸

Estimates of the average present value of future earnings, stratified by age and gender, were applied to the number of deaths in each age and gender category for each of the conditions. Due to the low number of reported deaths for many conditions, only those conditions with an unweighted cell count >5 deaths were used in calculating lost future earnings. Using this criterion, the conditions eligible for evaluation were nonmelanoma skin cancer, bullous diseases, cutaneous lymphoma, psoriasis, herpes simplex and zoster, lupus erythematosus, skin ulcers and wound healing, and melanoma.

Intangible Costs Due to Quality of Life Impact

Many skin conditions affect patients’ perception of quality of life. To estimate the burden of skin conditions on quality of life, scores from the Dermatology Life Quality Index (DLQI), a health-related quality of life questionnaire specifically focused on skin conditions, were collected from the literature for each of the disease categories.

The DLQI has been evaluated for repeatability, reliability, internal consistency, and sensitivity to change, and has been compared to other quality of life scales. It has been found to more accurately report the patient’s perspective on quality of life for these conditions than other non-dermatological scales. The DLQI scale ranges from 0, indicating no impairment of life quality, to 30, indicating maximum impairment. A review article of the DLQI published in 2004 provided the range and mean of means of all DLQI scores published in the literature in the last ten years.¹⁹

¹⁸ Compressed Mortality File 1979-1998 and 1999-2001. 2004; Atlanta, GA: Centers for Disease Control. Accessed January 14, 2005. www.wonder.cdc.gov.

¹⁹ Lewis V, Finlay AY. 10 years experience of the Dermatology Life Quality Index (DLQI). *J Investig Dermatol Symp Proc* 2004;9(2):169-80.

Among the diseases under study, DLQI scores were not available for actinic keratosis, benign neoplasms or keloid scars, cutaneous lymphoma, and melanoma. Since the correlation between DLQI scores and utility scores was found to be high ($r=-0.88$), a proxy DLQI score was computed for each of these skin conditions based on utility scores reported in the literature. Only three conditions, cutaneous drug eruptions, herpes simplex and solar radiation, did not have DLQI scores or utility values reported in the literature. As such, conservative estimates based on the quality of life considerations for conditions with similar manifestations were used to approximate the effects of these conditions of quality of life.

To estimate the burden of skin conditions on quality of life from an economic perspective, a willingness-to-pay approach was adapted to approximate the average amount that a person with a diagnosed skin condition would be willing to pay for a particular health outcome. In this case, the outcome was defined as relief from symptoms. These costs are considered separately from indirect costs because they do not represent actual expenditures, rather, these intangible costs approximate the intrinsic effect that these conditions have on overall health and quality of life.²⁰

From willingness-to-pay studies on atopic eczema, acne, and psoriasis found in the literature, a power curve with the equation $y=0.0148x^{4.6131}$ was estimated to predict the daily quality of life cost based on each condition's DLQI score.^{21,22} The average duration of illness per year for each condition was taken into account when calculating the annual willingness to pay. For chronic conditions such as acne, atopic dermatitis, psoriasis, and vitiligo, consideration was given to the amount of time per year during which the condition was active or in a state of flare-up. As the DLQI is symptom-focused, the willingness to pay estimates made from these scores are not indicative of a patient's threshold for paying for a cure, (which may be considerably higher than the values reported here, especially for life-threatening conditions).

Assessing Data Source Utility

After completing all analyses from the individual datasets, the reliability and validity of the data were assessed. The unweighted cell count for each variable, the overall geographic and age distribution of the dataset, and the methods used in sampling the population were all considered in selecting the definitive source for a given data point. Further, the exact phrasing of the questions asked of the sample population in the NHIS, where applicable, was considered in order to determine if there was the possibility of miscoding or misinterpretation.

²⁰ Gold 1996.

²¹ Lundberg L, Johannesson M, Silverdahl M, Hermansson C, Lindberg M. Quality of life, health-state utilities and willingness to pay in patients with psoriasis and atopic eczema. *Br J Dermatol* 1999 Dec;141(6):1067-75.

²² Parks L, Balkrishnan R, Hamel-Gariepy L, Feldman SR. The importance of skin disease as assessed by "willingness-to-pay." *J Cutan Med Surg* 2003;7(5):369-71.

Chapter 3: Skin Cancer, Precancerous Conditions and Benign Neoplasms

This chapter presents estimates of the clinical, epidemiological, and economic impacts of cancerous and precancerous skin conditions as well as benign neoplasms. Included in this group of conditions are actinic keratosis, melanoma, nonmelanoma skin cancer, cutaneous lymphoma and benign neoplasms such as keloid and hypertrophic scars.

Actinic Keratosis

Actinic keratosis (AK) is a precancerous skin lesion that appears and may feel scaly or rough in nature. An individual may have one or many AK lesions that, if left untreated, can progress into squamous cell carcinoma, a malignant type of skin cancer. Routine observation by a medical professional is recommended to determine if an AK lesion has progressed to a malignant state. The estimated probability of a lesion progressing to squamous cell carcinoma ranges widely, from less than 1% to 20% per lesion per year.²³ Individuals with AKs may experience symptoms such as itching, burning, and tenderness around the lesion. Other symptoms include pink, brown or red discoloration of the skin with a lesion diameter of less than 1 centimeter.

AKs may be caused by various biological and/or environmental factors. Biological factors that are known to influence AKs include age, gender, and skin color. Those at greatest risk of developing AKs are Caucasian males between the ages of 65 and 74. People who are immunocompromised or have mutations in the p53 tumor suppressor gene are also at an elevated risk of developing AKs.²⁴ Non-biological factors include occupational exposure to UV light, geographic place of birth, overall sun exposure, socioeconomic status, and diet.

Since most AKs are found on parts of the body that typically receive the greatest exposure to sunlight (i.e., backs of hands, forearms, head and neck), UV radiation is thought to be the major environmental contributor to AK. For this reason, behavioral modifications such as limiting sun exposure and increasing the application of sunscreen are considered to be the most effective prevention strategies. Treatment options for AKs include cryotherapy (freezing of the lesion), surgical removal, topical pharmaceuticals, and photodynamic therapy (use of light-sensitive chemicals and lasers to destroy cancer cells).

Epidemiology

The incidence of AK is not captured in the NHIS dataset, but the literature reports estimates from the 1974 NHANES dermatological survey. From this review it was determined that AK lesions more often affect males than females, and the likelihood of developing lesions increases with age across both sexes. The age adjusted prevalence for AK in the U.S. has been estimated at 6.5%, but for males with high sun exposure between the ages of 65 and 74,

²³ Gupta AK, Inniss K, Wainwright R, et al. Interventions for actinic keratoses (protocol for a Cochrane review). The Cochrane Library 2004;(3).

²⁴ Ibid.

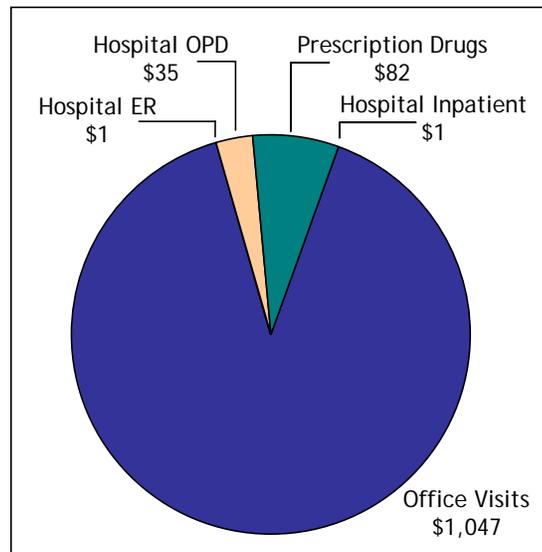
the rate climbs substantially to 55.4%. AKs are very common among adults ages 60 to 69, with 83% of men and 64% of women having at least one lesion.²⁵ These rates translate into a crude prevalence rate of 19,653 cases per 100,000 individuals. When this rate was age-adjusted and applied to the 2004 U.S. population, 58 million individuals were estimated to experience at least one AK lesion during a calendar year, with 26 million of these individuals age ≥ 65 . No deaths were reported due to AK in the 2002 Compressed Mortality File.

Direct Costs

The 2004 total direct cost for AK is estimated at \$1.2 billion (**Figure 3.1**). According to NAMCS data, AK lesions were predominantly treated in physician offices, with 7,852,900 visits made to these sites of care for this condition in 2004, accounting for \$1 billion, or 90%, of the total direct cost. Hospital outpatient departments and emergency rooms were less frequently accessed as sites of care, with 110,000 and 7,500 visits respectively, and a total cost of \$36.2 million (**Figure 3.6**). While there were no inpatient hospital stays with a primary diagnosis of AK, the costs of services and physician time in this setting were estimated at \$0.9 million for secondary diagnoses.

According to Scott-Levin data, prescription drugs specifically for AK accounted for \$81.8 million or 7% of the total costs. The OTC product data was not specific to products purchased for the treatment of AK. However, many products recommended for the treatment of AK, such as 5-fluorouracil cream, generally require a prescription. Additionally, as noted above, actinic keratosis is one of the diseases for which certain significant drug costs, (i.e., for drugs sold through specialty pharmacies), are not captured by the datasets used in this study.

Figure 3.1. Annual Direct Cost of Actinic Keratosis, U.S.
(\$ millions, 2004)



²⁵ Ibid 2004.

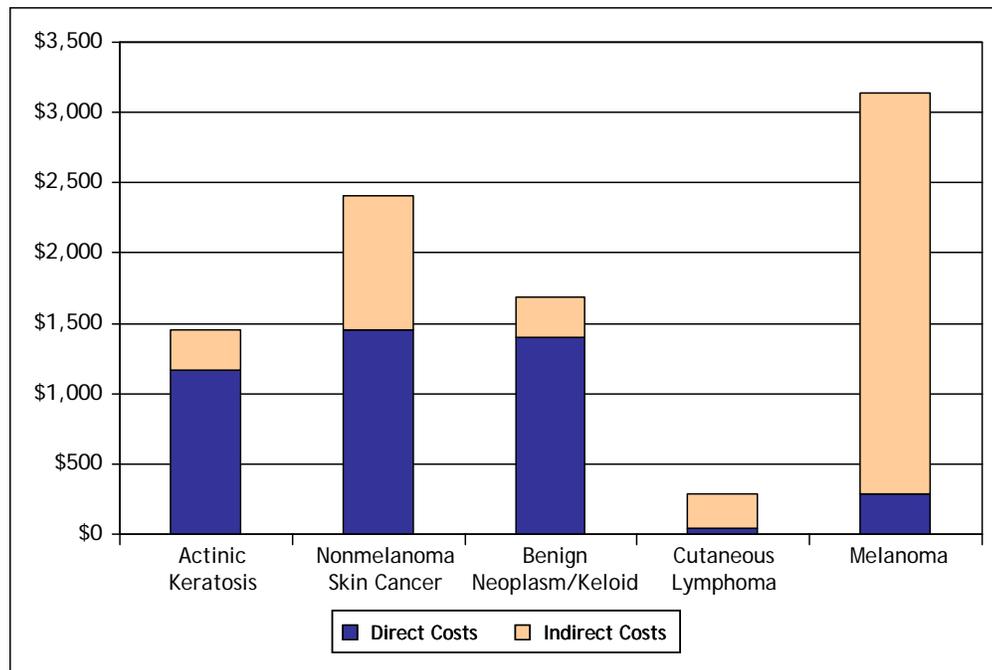
Indirect Costs

Total indirect costs associated with lost productivity for AK are estimated at \$286 million, including \$113 million in lost workdays and \$96 million in restricted activity days for individuals who have the condition. The remaining \$76 million is attributable to caregiver lost workdays, which, due to the higher prevalence of this condition in individuals age ≥ 65 , is more substantial than for conditions affecting younger individuals. Because AK is not a condition associated with mortality, there are no significant indirect costs associated with foregone future earnings due to premature death for this condition.

Intangible Costs Due to Quality of Life Impact

Since a study using the DLQI to estimate quality of life in AK patients was unavailable in the literature, a corresponding utility value was used to calculate a proxy DLQI (as described in Chapter 2). The proxy DLQI was found to be 3.6 on a scale of 0 (no impairment) to 30 (maximum impairment). This DLQI score was the lowest for all of the skin conditions under review in this study. To approximate quality of life, a willingness to pay approach was adopted, whereby the quality of life effects of a particular condition are monetarily quantified to indicate how much individuals with the condition are willing to pay for symptom relief. In other words, the greater the willingness to pay, the more substantial the effects of the condition on quality of life. While individuals with AK report lower relative quality of life impacts than other skin conditions under review in this study, the aggregate value for willingness to pay for symptom relief for all individuals with AK is substantial, at \$5.8 billion (Figure 3.2). This amount is mainly attributable to the high prevalence of AK.

Figure 3.2. Annual Direct and Indirect Cost of Skin Cancer and Precancerous Conditions, U.S. (\$ millions, 2004)



Melanoma

The most well-known form of skin cancer, melanoma, is also the most aggressive and deadly. In 2004, 7,900 of the approximately 55,000 individuals newly diagnosed with melanoma will die of their disease. In addition to its high mortality rate, melanoma is now the second leading cause of lost productive work years due to cancer.²⁶

Melanoma causes abnormal proliferation of specialized cells in the skin, eyes, and hair that produce the pigment melanin. According to the American Cancer Society (ACS), early diagnosis is the most important factor in successful treatment and ACS recommends annual skin examinations for everyone over the age of 40 and every three years for individuals between the ages of 20 and 40.²⁷ A clear relationship between increased sun exposure and risk for melanoma has been established. Therefore, preventive efforts to reduce the incidence of the disease focus on increasing application of sunscreens and protective clothing when outdoors, eliminating the use of tanning beds, and reducing sun exposure between the hours of 10am and 4pm (when UV rays are harshest). In addition to environmental factors, genetic factors contribute to risk for developing melanoma. Individuals with a family history of melanoma may have mutations in the CDKN2A and CDK4 genes, which confer a 60-90% lifetime risk of developing melanoma.²⁸

Typical warning signs of melanoma include pigmented skin lesions with abnormalities such as asymmetry, borders with irregular edges, variance in color, and a diameter of larger than 6 millimeters.²⁹ Moles and/or skin lesions that change color over time or bleed easily can also indicate developing melanoma. Diagnosis requires biopsy of the suspected lesion, which typically consists of removal of the entire lesion and a small margin of surrounding healthy tissue (generally 1mm-3mm). If melanoma is diagnosed following microscopic examination of the lesion, then further surgical removal of the surrounding tissue is recommended. Patient perception of the scarring following surgical resection of this tissue may influence quality of life, particularly if the scar is large or visible to others. Women and younger melanoma patients are more likely to experience significant anxiety or depression following removal of a melanoma.³⁰

For more advanced melanoma, radiation therapy, chemotherapy and/or immunotherapy may be recommended as an adjunct to surgical removal of the cancerous lesion. Diagnostic tests (e.g., lymph node biopsy and MRI scans) can be used to determine whether the cancer has spread to other organs (e.g., the lymph nodes, brain or liver) and are used to determine whether downstream therapy is warranted. Prognosis is typically poor for patients in

²⁶ Ibid 2004.

²⁷ Monitor your signs of skin cancer. Atlanta, GA: American Cancer Society, 1999. Accessed September 6, 2004. http://www.cancer.org/docroot/NWS/content/NWS_1_1x_Monitor_Your_Skin_for_Signs_of_Skin_Cancer.asp.

²⁸ Ibid.

²⁹ Howard S. Medline plus medical encyclopedia: melanoma. Bethesda, MD: U.S. National Library of Medicine and National Institutes of Health, 2003. Accessed September 7, 2004. <http://www.nlm.nih.gov/medlineplus/ency/article/000850.htm>.

³⁰ Newton-Bishop JA, Nolan C, Turner F, et al. A quality-of-life study in high-risk (thickness \geq or 2 mm) cutaneous melanoma patients in a randomized trial of 1-cm versus 3-cm surgical excision margins. *J Investig Dermatol Symp Proc* 2004;9(2):152-9.

which melanoma has metastasized to other organs or body tissues, with only 5% of patients surviving for more than five years.³¹

Epidemiology

Melanoma is one of the few skin conditions with comprehensive epidemiology statistics available in a nationally representative dataset. For this study, the NCI SEER database was used to estimate the incidence, prevalence, and mortality rates for melanoma, stratified by age and gender. Applying the most recent available SEER data for 2001 to the 2004 U.S. population, an estimated 55,100 individuals were diagnosed with melanoma and 7,910 deaths were attributable to this cancer in 2004. Furthermore, its reported incidence has increased 690% from 1950 to 2001, and the overall mortality rate has increased 165% during the same period. The overall crude prevalence rate for all ages and both sexes is roughly 240 per 100,000 individuals. When this rate is applied to the 2004 U.S. population, the overall prevalence of melanoma is 718,000 individuals.

Among all cancers in the U.S., the reported incidence of cutaneous melanoma ranks fifth among men and seventh among women. Melanoma is the most commonly diagnosed cancer among women ages 20-29.³² Individuals at highest risk for melanoma include those with fair skin, red or blonde hair, and those who are often and continuously exposed to sunlight (such as lifeguards and landscapers), who had multiple blistering sunburns as a child or adolescent, and/or with a family history of the disease.

Direct Costs

The estimated 2004 total direct cost associated with treatment of melanoma was \$291 million. This includes \$213 million in costs for care provided in hospital inpatient and outpatient departments, physicians' offices, and emergency rooms (**Figure 3.3**). There were 603,800 physician office visits due to melanoma, according to data from the National Ambulatory Medical Survey, making this the primary site of care for individuals with this condition. There were 57,000 visits made to hospital outpatient departments and 6,000 visits made to emergency rooms for melanoma (**Figure 3.6**).

Inpatient hospital stays where melanoma was listed as one of the diagnoses totaled 10,400, with nearly half of these visits listing melanoma as the primary diagnosis. Of those cases where melanoma was listed as the primary diagnosis, the average length of stay was 3.6 days, according to the NIS. Hospital inpatient costs for melanoma amounted to \$35.4 million.

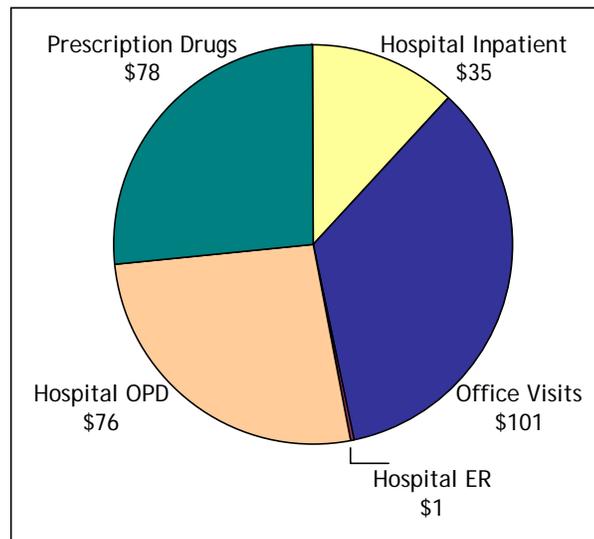
OTC products generally are not indicated in the treatment of melanoma, though they are used in the prevention of skin cancers including melanoma (see chapter 9). Prescription drugs specifically prescribed for the treatment of melanoma accounted for \$77.5 million of the total direct costs of this condition. Additionally, as noted above, melanoma is one of the diseases for which certain significant drug costs, (i.e., for drugs sold through specialty pharmacies), are not captured by the datasets used in this study.

³¹ Tsao 2004.

³² Ibid.

Cost-analyses in the literature indicate that the direct costs of melanoma rise steeply with increasing severity of disease. A study published in 1998 found that 90% of the direct costs of care for melanoma were attributable to the 20% most severe cases.³³ It also found that the average total cost of care for a patient with localized, non-invasive melanoma was approximately \$1,310 (in 1997 U.S. dollars), compared to the cost of care for a patient with distant metastases and lymphatic involvement, which was \$42,410 during the same time period. Terminal care for those patients with advanced melanoma accounted for the largest portion of the total direct cost of melanoma, constituting almost 35% of the total cost.

Figure 3.3. Annual Direct Cost of Melanoma, U.S.
(\$ millions, 2004)



Indirect Costs

The indirect costs associated with melanoma are particularly high, at an estimated \$2.9 billion in annual lost productivity alone (**Figure 3.2**). The majority of this lost productivity is due to forgone future earnings due to premature death, since as many as 45% of melanoma deaths occur prior to retirement age. Due to its high incidence in younger individuals, melanoma is the second largest cause of lost productive years for all types of cancer.³⁴ The average net present value of foregone future earnings due to premature death is approximately \$364,000.

Intangible Costs Due to Quality of Life Impact

The average DLQI score for individuals with melanoma is 4.1 on a scale of 0 (no impairment) to 30 (maximum impairment). This DLQI score is less than that for acne (DLQI=11.9), atopic dermatitis (DLQI=12.2), and psoriasis (DLQI=8.8). This may reflect the nature of the DLQI instrument, which asks a series of questions about the effects of the condition on specific situations such as feeling embarrassed about the condition, or the condition interfering with activities such as playing sports or engaging in social activities.

³³ Tsao H, Rogers GS, Sober AJ. An estimate of the annual direct cost of treating cutaneous melanoma. *J Am Acad Dermatol* 1998;38(5 Pt 1):669-80.

³⁴ Tsao H, Atkins MB 2004.

As such, individuals with melanoma, especially early-stage melanoma, might not experience significant physical limitations due to their condition or have few outward symptoms that would prompt negative social attention.

To describe the effects of this condition in a monetary context, a willingness to pay approach was adopted, whereby the quality of life effects of a particular condition are quantified to indicate how much individuals with the condition are willing to pay for symptom relief. That is, the greater the willingness to pay, the more substantial are the effects of the condition on quality of life. Using the DLQI, the average amount that an individual with melanoma would be willing to pay for symptom relief is estimated at \$1,005 per year. This amount is not reflective of how much an individual with melanoma would pay to be *cured* of their condition; the amount for a cure likely would be substantially higher, especially considering the mortality rate of this condition. When adjusted for disease severity and applied to the entire population of individuals with melanoma, the collective willingness-to-pay for symptom relief for this condition is \$367 million annually.

Cutaneous T-Cell Lymphoma

Cutaneous lymphoma encompasses several disorders with varying presentations and treatment options. While all lymphomas originate in lymphocytes, which are found throughout the body, cutaneous lymphomas are specific to lymphocytes of the skin. Cutaneous T-cell lymphoma (CTCL) typically originates in T-lymphocytes, a type of white blood cell. The most common type of CTCL, known as mycosis fungoides (MF), produces a variety of skin manifestations. Another type of CTCL is Sezary syndrome, a less common yet considerably more aggressive disease that causes malignant lymphocytes to circulate in an individual's bloodstream, spreading the disease to other organs.

Symptoms of CTCL may include a dry or scaly skin rash, and dark or discolored patches on the skin. Clusters of small, red bumps are also a common sign of CTCL. Because they resemble other skin disorders, these clusters are frequently misdiagnosed as psoriasis or contact dermatitis. Individuals with CTCL may also experience itching, that in some cases is so severe it interferes with an individual's ability to sleep.³⁵ Unlike melanoma and other skin cancers that are most commonly found on parts of the body that are most often exposed to the sun, CTCL is usually found on body surfaces that are not commonly sun-exposed (e.g., breasts and buttocks), though any skin surface may be affected. In addition to the effects on the skin, CTCL can spread from the skin to internal organs and lymph nodes via the lymphatic system.³⁶ The causes of CTCL are not well understood, but both environmental and genetic factors are suspected.

The multiple treatment options for CTCL include topical pharmaceuticals, radiation therapy, photodynamic therapy, chemotherapy, photochemotherapy, and immunotherapy. The prognosis for patients with CTCL depends on several factors, such as the age of the patient, type of disease and the stage of disease progression. For example, median survival of patients with the highly aggressive Sezary syndrome is 32 months from the time of

³⁵ FS-5 cutaneous T-cell lymphoma. White Plains, NY: The Leukemia and Lymphoma Society, 2004. Accessed 7 September 2004. http://www.leukemia-lymphoma.org/all_mat_toc.adp?item_id=9846&cat_id=1215.

³⁶ Ibid.

diagnosis. For primary CTCL, which only involves the skin, the median survival time is much improved, with a five-year survival rate of 96% or more.³⁷

Epidemiology

Of all the skin conditions reviewed in this study, incidence of CTCL is the lowest, with approximately 1,500 new cases diagnosed per year, according to estimates from the Leukemia and Lymphoma Society.³⁸ From the literature, incidence rates for MF, the most common form of CTCL, were reported at 0.36 cases per 100,000 person-years.³⁹ In fact, the incidence rate of CTCL is low enough to meet coverage criteria established by the Orphan Drug Act of 1983, which provides incentives for research into treatment options for diseases with small patient populations.⁴⁰ Certain population subgroups have differential risks for developing CTCL. Men are reported to be twice as likely as women, and African Americans are more likely than Caucasians, to develop the disease. Risk of developing CTCL increases with age, particularly for individuals over the age of 60.⁴¹

Prevalence statistics for cutaneous lymphoma are not available in nationally representative datasets, largely due to its low incidence. There were also no studies found in the literature that estimate the prevalence of CTCL. For this reason, an approximation of the prevalence of CTCL was made based on the average length of survival and the reported incidence rate found in the literature. Based on an average length of survival of 10 years and a combined incidence rate of 0.9 cases per 100,000 people for mycosis fungoides and Sezary syndrome, the crude prevalence rate is estimated at 9 cases per 100,000 people. When applied to the 2004 U.S. population, only 24,900 individuals are affected by CTCL in a calendar year, the lowest prevalence of all skin conditions under review in this study.

According to the Compressed Mortality File of the CDC, there were 742 deaths due to CTCL in 2002. The majority of these occurred in the population age ≥ 65 , with 251 male and 194 female deaths recorded in this age category. According to a 1999 mortality study on MF, the male-to-female mortality rate ratio was 1.8.⁴² Additional research has suggested that the reported mortality due to MF may be as much as 40% lower than actual mortality.⁴³

Direct Costs

The total direct cost associated with treatment of CTCL is \$44 million (**Figure 3.4**). Nearly 40% of this total cost is attributable to prescription drugs, estimated to be \$16 million. As noted above, actinic keratosis is one of the diseases for which certain significant drug costs, (i.e., for drugs sold through specialty pharmacies), are not captured by the datasets used in

³⁷ Whittaker SJ, Marsden JR, Spittle Met al. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. *Br J Dermatol* 2003;149(6):1095-1107.

³⁸ FS-5 cutaneous T-cell lymphoma 2004.

³⁹ Girardi M, Heald PW, Wilson LD. The pathogenesis of mycosis fungoides. *N Engl J Med* 2004;350(19):1978-88.

⁴⁰ FS-5 cutaneous T-cell lymphoma 2004.

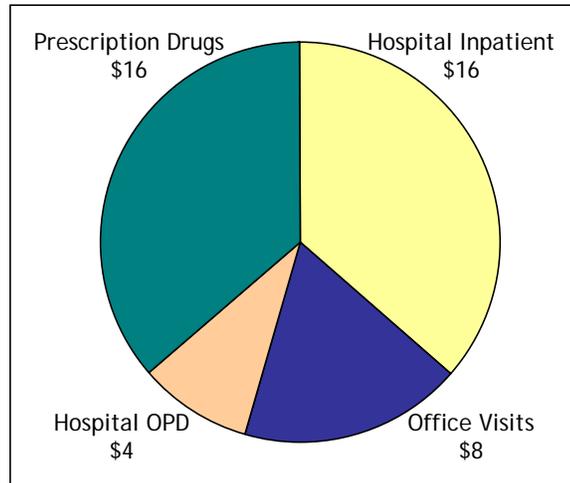
⁴¹ Whittaker 2003.

⁴² Weinstock MA, Gardstein B. Twenty-year trends in the reported incidence of mycosis fungoides and associated mortality. *Am J Public Health* 1999;89(8):1240-4.

⁴³ Weinstock MA, Reynes JF. Validation of cause-of-death certification for outpatient cancers: the contrasting cases of melanoma and mycosis fungoides. *Am J Epidemiol* 1998;148(12):1184-6.

this study. The remaining costs are attributable to care provided in inpatient settings, physicians offices, hospital outpatient departments and emergency rooms. For individuals with CTCL, the most common site of care is the physician office, with 102,300 visits in 2004. Hospital outpatient departments followed in utilization with 41,000 visits. CTCL was listed as the primary diagnosis for inpatient hospital stays in only 2,900 cases, but was listed as a non-primary diagnosis in 6,600 cases (**Figure 3.6**).

Figure 3.4. Annual Direct Cost of Cutaneous Lymphoma, U.S.
(\$ millions, 2004)



Indirect Costs

The estimated total indirect cost associated with CTCL due to lost productivity is \$242 million annually (**Figure 3.2**). The majority of this lost productivity (\$236 million) is in the form of foregone future earnings due to premature death. Due to the higher mortality rate for this condition in the population age ≥ 65 , (among whom 59% of all deaths attributable to CTCL occurred), the net present value of foregone future earnings for individuals was only \$308,124. Data limitations for this disease prevented further delineation of lost productivity into lost workdays, restricted activity days, and caregiver lost workdays.

Intangible Costs Due to Quality of Life Impact

A study using the DLQI for individuals with cutaneous lymphoma was not available in the literature, so a DLQI score was approximated from reported utility scores (see Chapter 2 for methods). The approximated DLQI score for cutaneous lymphoma was 16.4 on the 0-30 scale. The willingness-to-pay for symptom relief for individuals with cutaneous lymphoma is \$3,560, the largest amount for all skin conditions considered in this study. However, due to its extremely low prevalence, the aggregate willingness-to-pay for all individuals with CTCL is only \$9 million.

Nonmelanoma Skin Cancer

Two of the most common forms of skin cancer, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are collectively known as nonmelanoma skin cancer. BCC and SCC develop in the epidermal layer of the skin, usually the result of repeated exposure to UV radiation.⁴⁴

Basal Cell Carcinoma

BCC is the most common type of cancer found in humans.⁴⁵ BCC lesions are not uniform and may appear as a thickening of the skin or a red patch, or a wound that fails to heal. BCCs grow locally and are less likely to metastasize compared to other types of skin cancer, but their growth can still be destructive to adjacent body tissues, including surrounding bones and muscles. BCCs typically appear on the head and neck, whereas melanomas can occur on either sun-exposed or sun-protected areas.

Persons at an increased risk for developing BCC are similar to those at an increased risk for developing melanoma, including individuals with red or blonde hair, with blue or green eyes, who experienced childhood sunburns, and who have a family history of skin cancer. BCC can occur in individuals who are undergoing immunosuppressive treatment or who have ingested arsenic.⁴⁶ While both environmental and genetic factors have been linked to the development of BCC, the greatest causative factor is thought to be exposure to UV radiation, especially through sun exposure during childhood and adolescence. Other contributing environmental factors may include occupational or therapeutic exposure to ionizing radiation, a diet that is high in fat and low in vitamins, and fiberglass dust.⁴⁷ Besides a positive family history for skin cancer, individuals with genetic pigment conditions such as albinism, xeroderma pigmentosa, and Gorlin's syndrome, are also at increased risk for developing BCC.⁴⁸

The primary treatment approach for BCC involves surgical removal or destruction of the lesion. Other treatment options include cryosurgery, Mohs micrographic surgery (in which a dermatologist removes the cancerous lesion layer by layer, examining each cross-section for cancer cells), radiation therapy, topical pharmaceuticals, photodynamic therapy, and immunotherapy. Treatment is generally successful with five-year cure rates exceeding 95%.⁴⁹

⁴⁴ Stulberg DL, Crandell B, Fawcett RS. Diagnosis and treatment of basal cell and squamous cell carcinoma. *Am Fam Physician* 2004;70(8):1481-88.

⁴⁵ Bath-Hexell FJ, Bong J, Perkins W, Williams HC. Interventions for basal cell carcinoma of the skin: systematic review. *BMJ* 2004;329(7468):705.

⁴⁶ Wong CS, Strange RC, Lear JT. Basal cell carcinoma. *BMJ* 2003; 327(7418):794-8.

⁴⁷ Gallagher RP, Bajdik CD, Fincham S, et al. Chemical exposures, medical history, and risk of squamous and basal cell carcinoma of the skin. *Cancer Epidemiol Biomarkers Prev* 1996;5(6):419-24.

⁴⁸ Wong 2003.

⁴⁹ *Ibid.*

Squamous Cell Carcinoma

Approximately 20% of all skin cancers are SCCs.⁵⁰ While AKs are thought to be early-stage SCC, relatively few AKs progress to SCC. The number of AKs that do progress to SCC is unknown, though estimates range from less than 1% to 20%.⁵¹ Although many AKs appear on the hands and forearms, SCCs are most likely to occur on the head and neck.⁵² Individuals who have multiple AKs or those who live in certain areas with hot and dry conditions (e.g., the southwestern U.S.) are at higher risk for having their AKs progress to SCCs.

The causes of SCC include environmental and biological factors. The main cause, though, is long-term overexposure to UV radiation. The biological risk factors for other skin cancers such as melanoma or BCC (e.g., individuals with fair skin, light eyes and red or blonde hair) similarly apply to SCC. Individuals who sunburn instead of tan and those who freckle easily are also more likely to develop SCC. Like melanoma, SCC is capable of metastasizing. SCC lesions are at high risk for metastasizing when they grow rapidly, are larger than 2 centimeters, are a relapse of a previously treated lesion, extend deeper than 6 millimeters into the skin, or are located on the ear, nose, and/or lip.⁵³ Treatment modalities for SCC are similar to those of BCC.

Epidemiology

Epidemiology statistics for basal and squamous cell carcinoma are generally excluded from nationally representative datasets such as the SEER database. Therefore, prevalence for nonmelanoma skin cancer was estimated using information from the American Cancer Society. To capture the relationship between increasing incidence and advancing age, age-specific incidence rates reported by the National Cancer Registry were applied to the ACS data. Based on these approximations, the crude prevalence of nonmelanoma skin cancer is roughly 450 cases per 100,000 individuals. Applying this rate to the 2004 U.S. population yields an estimated 1.2 million individuals with nonmelanoma skin cancer per year, 59% of whom are age ≥ 65 .

Reports in the literature suggest that the incidence of nonmelanoma skin cancer has increased steadily since the 1970s, mostly due to increases in sun exposure and the use of artificial tanning lamps.⁵⁴ BCC is more frequently observed in Caucasians, with an overall lifetime risk of 30% for this population. Individuals with dark skin rarely experience BCC. The risk of developing BCC increases with age and is more frequently observed in men.⁵⁵ The incidence of BCC varies geographically depending on latitude and level of UV exposure. In the U.S., the incidence of BCC is approximately 146 per 100,000 people. In

⁵⁰ What is non-melanoma skin cancer? Atlanta, GA: American Cancer Society, 2004. Accessed October 8, 2004 http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_is_skin_cancer_51.asp?sitearea=CRI&viewmode=print&.

⁵¹ Gupta AK, Inniss K 2004.

⁵² Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. *J Am Acad Dermatol* 2000;42(1 Pt 2):4-7.

⁵³ Ibid.

⁵⁴ Stulberg 2004.

⁵⁵ Wong 2003.

contrast, the incidence is 788 cases per 100,000 population in Australia, where the average amount of sun exposure is much greater than in other parts of the world.⁵⁶

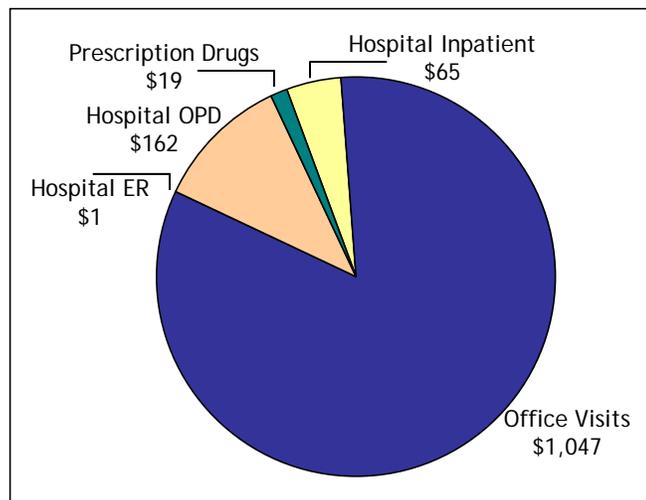
Approximately 200,000 new SCCs are diagnosed annually, of which 1,300-2,300 cases will be fatal. The risk for developing SCC is highest for Caucasian males, who have an estimated lifetime chance of 9-14% of developing this disease.⁵⁷ The CDC Compressed Mortality File indicates that there were 3,500 deaths attributable to nonmelanoma skin cancer in 2002. Of these, 75% occurred in the population age ≥ 65 .

Direct Costs

The direct cost associated with treatment for nonmelanoma skin cancer is \$1.5 billion annually (**Figure 3.5**). The bulk of this, \$1.2 billion, is attributed to care received in physician offices. In 2004, there were nearly 1.8 million visits to physician offices for nonmelanoma skin cancer, making it the most frequently used site of service for this condition. Hospital outpatient departments were used 63,000 times at a cost of \$162 million. There were 10,800 inpatient hospital stays primarily attributable to nonmelanoma skin cancer, and 22,500 stays where this condition was listed as a non-primary diagnosis (**Figure 3.6**). Inpatient hospital stays for this condition were responsible for \$65 million, or roughly 4% of the total cost.

Prescription drugs for nonmelanoma skin cancer only amounted to slightly more than 1% of the total direct cost, reflecting that treatment for this condition is primarily procedure-based (e.g., surgical excision, biopsy). However, as noted above, nonmelanoma skin cancer is one of the diseases for which certain significant drug costs, (i.e., for drugs sold through specialty pharmacies), are not captured by the datasets used in this study.

Figure 3.5. Annual Direct Cost of Nonmelanoma Skin Cancer, U.S.
(\$ millions, 2004)



⁵⁶ Wong 2003.

⁵⁷ Salasche 2000.

Indirect Costs

Total indirect costs associated with lost productivity for nonmelanoma skin cancer are estimated at \$961 million, most of which (\$893 million) is attributable to lost future earnings due to premature death (**Figure 3.2**). The age distribution of nonmelanoma skin cancer has a demonstrable effect on the type of lost productivity from this disease. Restricted activity days, including those days during which an individual who is not participating in the workforce (such as a retiree) is affected by their condition, account for \$25 million of the lost productivity, with caregiver lost workdays accounting for \$18 million. The remaining \$25 million is attributable to lost workdays for individuals who have the condition.

Intangible Costs Due to Quality of Life Impact

The average score on the DLQI for individuals with BCC is 4.8 on a scale of 0-30. Due to the similarities between basal and SCC, this DLQI score was applied to both conditions. Based on DLQI, individuals with nonmelanoma skin cancer report experiencing greater impairment to their quality of life than individuals with actinic keratosis (DLQI=3.6) but less than that of individuals with cutaneous fungal infections (DLQI=5.5). Using a willingness-to-pay perspective and adjusted for disease severity, this DLQI score indicates that the average willingness-to-pay for an individual with nonmelanoma skin cancer for symptom relief was approximately \$1,005 per year. Therefore, the aggregate annual value of willingness-to-pay for all individuals with nonmelanoma skin cancer was \$125 million.

Benign Neoplasms

Scars are a type of benign neoplasm that often form in response to significant trauma such as burns or surgical incisions. In some individuals, substantial scarring may also occur following relatively insignificant injuries such as a needle puncture for vaccinations or ear piercing. When the body produces more scar tissue than is necessary to close and protect a wound, the scar is referred to as a keloid or hypertrophic scar. Keloid scars form when scar tissue begins to encroach on normal tissue, resulting in an irregular and oftentimes disfiguring mass on the skin. Keloids tend to form following superficial injury, such as an insect bite. Hypertrophic scars can be equally as disfiguring as keloids, but are confined to the site of injury and do not infringe on the surrounding skin. Hypertrophic scars usually form after more serious injuries to the skin such as severe burns or surgical incisions. Both types of scars may be physically painful and/or itchy.

Keloid and hypertrophic scars, especially those on the head and neck, may cause psychosocial distress, though these scars are rarely life-threatening. Surgical removal of keloid scars is one treatment option, though 50-80% of patients who undergo this surgery develop a new and sometimes larger keloid scar.⁵⁸ Other treatment options include steroid injections, cryotherapy, laser therapy, pressure therapy, corticosteroid treatment, or radiation therapy. Since treatment of these scars can be especially challenging, prevention in the form of limiting nonessential surgical procedures in individuals known to form keloids or hypertrophic scars is a critical preventive measure.

⁵⁸ Salasche 2000.

Epidemiology

The NHIS did not collect prevalence data on benign neoplasms. Therefore, prevalence estimates were obtained from the literature, which indicated that keloid scars form following 5-15% of all wounds, and occur in approximately 10% of the population (approximately 10,000 cases per 100,000 individuals).⁵⁹ Risk factors for keloid scarring include having a dark complexion, and it is estimated that between 4.5 and 16% of individuals of African and Hispanic descent experience keloid scars.⁶⁰ Individuals with dark complexions are more prone to keloid and hypertrophic scars.⁶¹

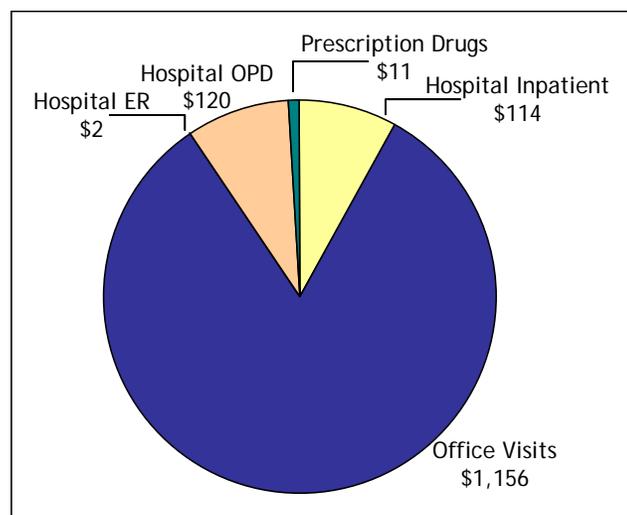
Benign neoplasms do not usually result in death, with a mortality rate of only 0.009 per 100,000 people. The CDC's Compressed Mortality File reported only 23 deaths due to benign neoplasms in 2002.

Direct Costs

Direct costs associated with treatment of benign neoplasms totaled \$1.4 billion (**Figure 3.6**). Visits to physician offices accounted for \$1.2 billion, or 86% of the total direct cost. Benign neoplasms were also treated in hospital outpatient departments, with more than 216,700 visits paid to this site of service at a cost of \$120 million (**Figure 3.7**). Costs associated with inpatient hospital stays were estimated at \$114 million, with more than 14,700 cases listing benign neoplasms as the primary diagnosis.

Prescription drugs for benign neoplasms accounted for nearly \$11 million of the total cost, emphasizing that care for these conditions relies heavily on procedures. However, as noted above, benign neoplasms are one of the diseases for which certain significant drug costs, (i.e., for drugs sold through specialty pharmacies), are not captured by the datasets used in this study.

Figure 3.6. Annual Direct Cost of Benign Neoplasms, U.S.
(\$ millions, 2004)



⁵⁹ O'Brien 2004.

⁶⁰ Alster TS, Tanzi EL. Hypertrophic scars and keloids: etiology and management. *Am J Clin Dermatol* 2003;4(4):235-43.

Indirect Costs

The indirect costs associated with lost productivity and forgone future earnings for benign neoplasms are estimated at \$281 million (**Figure 6.2**). Since only a crude prevalence rate was available for this condition, lost productivity costs cannot be reliably allocated into lost workdays, caregiver lost workdays, or restricted activity days. Foregone future earnings due to premature death from benign neoplasms totaled \$7.3 million, with an average of \$306,500 per individual death.

Intangible Costs Due to Quality of Life Impact

Benign neoplasms are known to affect quality of life for individuals with the condition due to physical and psychosocial factors. For example, if the neoplasm is located near a joint, movement may be restricted, impairing daily activities. Individuals with benign neoplasms have also expressed feelings of shame or distress due to their condition. Since quality of life studies using the DLQI were not available in the literature, a proxy score was estimated from reported utility values (see Chapter 2: Methods). The approximation yielded a DLQI score of 4.0.

To describe the effects of this condition in a monetary context, a willingness to pay approach was adopted, whereby the quality of life effects of a particular condition are quantified to indicate how much individuals with the condition are willing to pay for symptom relief. In other words, the greater the willingness to pay, the more substantial the effects of the condition on quality of life. When the DLQI score of 4.0 was applied to the willingness-to-pay algorithm, the yearly average willingness-to-pay was \$1,000 for symptom relief for an individual with a benign neoplasm. When considered for all individuals with benign neoplasms and weighted according to clinical severity, the overall willingness to pay for symptom relief for this condition is \$1.6 billion annually.

Figure 3.7. Health Care Utilization for Skin Cancer and Precancerous Conditions

| Disease | Inpatient Hospital Stays | Inpatient Hospital Stays (primary diagnosis only) | Outpatient Hospital Visits | Emergency Room Visits | Physician Office Visits |
|---------------------------|--------------------------|---------------------------------------------------|----------------------------|-----------------------|-------------------------|
| Actinic keratosis | 7,400 | - | 110,000 | 7,500 | 7,852,900 |
| Melanoma | 10,400 | 5,000 | 57,000 | 6,000 | 603,800 |
| Cutaneous T-cell lymphoma | 6,600 | 2,900 | 41,000 | 2,400 | 102,300 |
| Nonmelanoma skin cancer | 22,500 | 10,800 | 63,100 | 6,400 | 1,779,800 |
| Benign neoplasms | 36,000 | 14,700 | 216,700 | 9,900 | 6,763,700 |

Source: 2002-2003 NAMCS, NHAMCS, NHIS, NHDS adjusted to the 2004 U.S. population

⁶¹ Ibid.

Chapter 4: Dermatitis

This chapter presents estimates of the clinical, epidemiological and economic impacts of dermatitis conditions. This heterogeneous group of diseases includes contact dermatitis, atopic dermatitis (commonly referred to as eczema), and seborrheic dermatitis.

Contact Dermatitis

Contact dermatitis is a skin inflammation caused by direct contact with an irritating or allergenic substance. The site of contact may exhibit redness, blisters, cracks, scales, hives, and/or excessive dryness. The sensations associated with contact dermatitis often include itching, burning, and stinging of affected areas.

While many forms of contact dermatitis may appear clinically similar they are caused by different types of agents. Irritant contact dermatitis (ICD), resulting from environmental or occupational chemical exposures, is considered to be the most common type, followed by allergic contact dermatitis (ACD), caused by exposure to a substance to which an individual has become hypersensitive or allergic, which causes about 5-20% of all cases.⁶² Chemicals causing contact dermatitis are not exclusively irritant or allergenic in nature, and the physical manifestation of irritant and allergic contact dermatitis may be indistinguishable. However, patch testing, a diagnostic technique, allows clinicians to differentiate between these types of contact dermatitis. In the workplace, contact dermatitis has been reported as 80% irritant type and 20% allergic, but recent patch test studies of occupational contact dermatitis indicate that more than 50% of cases may be allergic.⁶³

Direct chemical exposure to the skin causes damage that can result ICD. Severity of ICD ranges broadly from “dishpan hands” to severe injuries resembling burns. Cumulative irritation, which develops after repeated exposure to a mild irritant (e.g., soaps, detergents, and household chemicals), is the most common cause of ICD. Determinants of hyperirritable contact dermatitis are numerous, including age, genetics, environment, and other associated skin diseases.⁶⁴ However, as with many other skin diseases, individual susceptibility and reaction to irritants is highly variable. Given sufficient incidence of exposure and appropriate concentration, almost all individuals can develop ICD. The most effective treatment of ICD is avoidance of exposure. The use of topical corticosteroids and emollients can provide symptomatic relief.

ACD develops when an individual becomes sensitized to an allergen and the immune system responds to the localized area of skin contact. Subsequent exposures then result in flare-ups. More than 3,000 environmental allergens have been reported to cause ACD, including corticosteroids, metals, preservatives, animal dander, cosmetics, and textiles.

⁶² Rietschel RL, Fowler JF. Fisher's Contact Dermatitis. 4th ed. Baltimore (MD): Williams and Wilkins; 1995.

⁶³ Beltrani VS, Boguniewicz M. Atopic dermatitis. *Dermatol Online J* 2003;9(2):1.

⁶⁴ Belsito DV. Patch testing with a standard allergen ("screening") tray: rewards and risks. *Dermatol Ther* 2004;17(3):231-9.

Management of contact dermatitis involves identification and avoidance of the causative agents. Patch testing can help health practitioners and patients identify specific allergens/allergen types to avoid. Topical corticosteroids, moisturizing products and oral antihistamines are often used to alleviate the symptoms of ACD. In severe cases, systemic administration of corticosteroids may be necessary.

Epidemiology

Prevalence estimates for these conditions were obtained from the peer-reviewed literature, as the 1996 NHIS did not collect data specific to contact, atopic and seborrheic dermatitis. Prevalence estimates for this group of diseases vary widely in the literature, mainly due to differing definitions of contact dermatitis and classification of ACD and ICD. For individuals under the age of 18, the prevalence rate for ACD was reported at 15% and prevalence for those over 18 was cited as 28%.^{65,66} The overall period prevalence rate for contact dermatitis was therefore estimated to be 24,400 cases per 100,000 individuals per year. When these rates were applied to the 2004 population, over 72 million individuals were estimated to have experienced at least one episode of contact dermatitis during the calendar year.

The prevalence of contact dermatitis is known to vary considerably by occupation. People who are frequently exposed to “triggers” of contact dermatitis as part of their jobs are more vulnerable to the condition. The literature has suggested that contact dermatitis is responsible for 86-97% of cases of occupational skin disease, which is the second highest cause of work-related disease in the U.S. and manifests in approximately 0.5 to 1.9 cases per full-time worker per year.⁶⁷

Contact dermatitis is virtually never life-threatening, with mortality rates lower than 1 person per 100,000 per year, as reported by the CDC Compressed Mortality File for 2002.

Direct Costs

The total direct cost associated with treatment for contact dermatitis is \$1.6 billion (**Figure 4.1**). According to Scott-Levin data, prescription drugs account for much of the costs of treating contact dermatitis, with more than \$747 million or 46% of total costs. Due to limitations of linking OTC product data to particular skin conditions, OTC costs associated with contact dermatitis could not be specified. However, OTC products such as skin creams and lotions are frequently used to treat mild cases of dermatitis (see Chapter 9). While unavailable, OTC costs specifically for contact dermatitis are likely substantial and a leading cost category for this disease.

Physician offices are the primary site of care for these patients, with more than 10.6 million visits related to contact dermatitis in 2004 (**Figure 4.5**). The total cost associated with these visits for physician time and services was \$657 million. In comparison, hospital outpatient

⁶⁵ Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Contact allergy and allergic contact dermatitis in adolescents: prevalence measures and associations. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS). *Acta Derm Venereol* 2002;82(5):352-8.

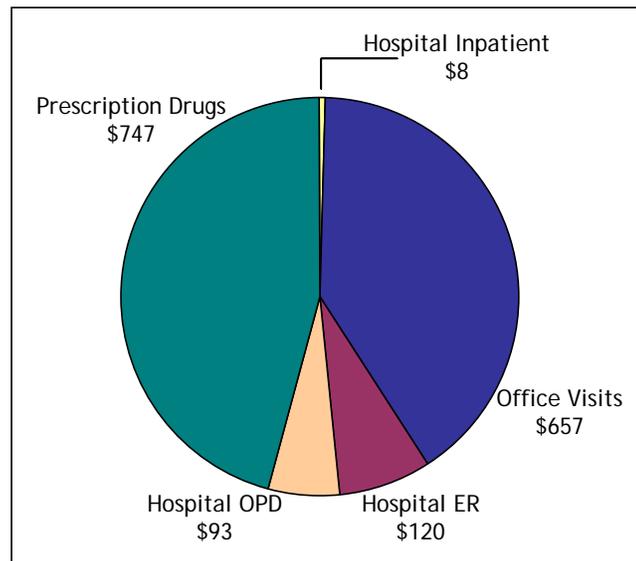
⁶⁶ Schafer T, Bohler E, Ruhdorfer S, Weigl L, Wessner D, Filipiak B, Wichmann HE, Ring J. Epidemiology of contact allergy in adults. *Allergy* 2001 Dec;56(12):1192-6.

⁶⁷ Koch P. Occupational contact dermatitis: recognition and management. *Am J Clin Dermatol* 2001;2(6): 353-65.

departments and hospital emergency rooms were utilized relatively infrequently, for a total of 1.7 million visits. Collectively, care provided in outpatient settings accounted for more than \$870 million of the total direct cost.

Hospital inpatient stays, where contact dermatitis is listed as the primary diagnosis, are relatively rare, accounting for only 2,500 stays in 2004 with an average length of stay of 3 days. However, as the non-primary diagnosis upon admission, contact dermatitis was identified in nearly 60,000 admissions in 2004. The total cost for contact dermatitis in the inpatient setting is only \$8.0 million, or less than 1% of the total direct cost of \$1.6 billion.

Figure 4.1. Annual Direct Cost of Contact Dermatitis, U.S.
(\$ millions, 2004)



Indirect Costs

Because mortality associated with contact dermatitis is low (less than 1 death per million individuals per year), indirect costs predominately result from lost productivity and diminished quality of life. Work, school, activities of daily living and social activities are all adversely affected by contact dermatitis, resulting in missed work days, loss of productivity and avoidance of social engagements. Mental health and vitality can be impaired in contact dermatitis patients during flare-up periods.⁶⁸

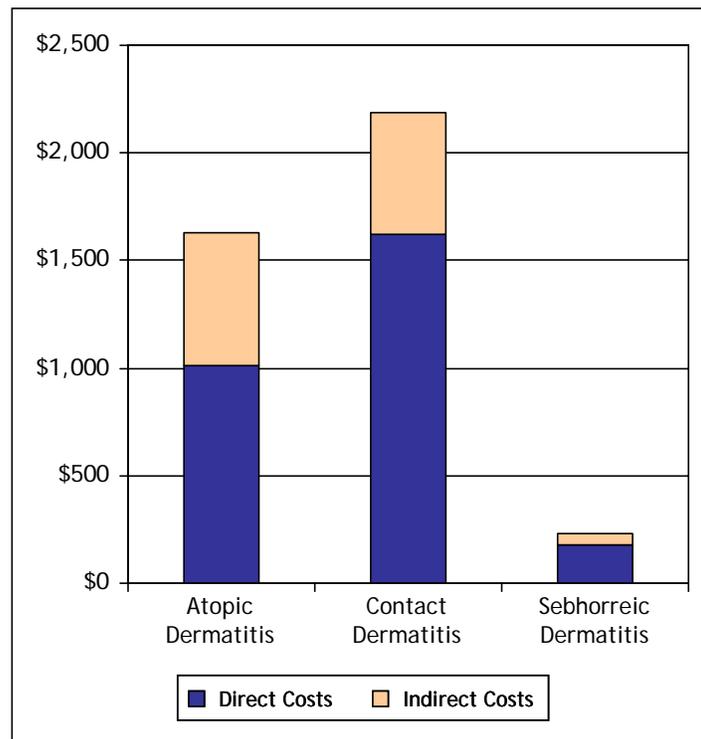
Indirect costs due to lost productivity for contact dermatitis are an estimated \$566 million, including \$295 million due to lost workdays for those affected by the condition, \$99 million associated with lost caregiver workdays and \$172 attributable to restricted activity days (Figure 4.2). This figure may underestimate indirect costs, since some individuals with mild/moderate contact dermatitis may not seek medical attention.

⁶⁸ Koch P. Occupational contact dermatitis: recognition and management. *Am J Clin Dermatol* 2001;2(6): 353-65.

Intangible Costs Due to Quality of Life Impact

The mean reported score on the DLQI for contact dermatitis is 7.5 (on a scale of 0-30), meaning that those affected by this condition experience a reduction in quality of life greater than those with actinic keratosis (DLQI=3.6), but less than that of cutaneous lymphoma (DLQI=16.4). At the individual patient level, those affected by this condition have an average willingness-to-pay of \$2.90 per symptomatic day. The aggregate annual willingness-to-pay for symptom relief by sufferers of contact dermatitis is estimated to exceed \$1.95 billion dollars.

Figure 4.2. Annual Direct and Indirect Cost of Dermatitis, U.S.
(\$ millions, 2004)



Atopic Dermatitis

Atopic dermatitis, commonly known as eczema, is a chronic, recurrent, inflammatory skin disease characterized by extremely itchy patches of skin. Scratching often leads to redness, swelling, cracking, “weeping” clear fluid, crusting, and scaling of the skin.⁶⁹ These itchy patches can appear anywhere on the body, including around the eyes and on the eyelids, but mainly occur on the scalp and face, especially the cheeks.

Although the cause of AD is unknown, the disease likely results from a combination of genetic and environmental factors, skin barrier defects, heightened susceptibility to

⁶⁹ Atopic dermatitis (a type of eczema) [handout on health]. Bethesda, MD: National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2003. Accessed October 20, 2004. <http://www.niams.nih.gov/hi/topics/dermatitis/index/html>.

infection, and malfunction of the immune system.⁷⁰ The genetic link between AD and respiratory illness can be especially strong. Children are much more likely to develop AD if one or both parents have a history of either AD or an allergic condition. These AD patients are also more prone to developing allergic conditions of their own. About 50% of AD patients, especially those with severe AD, will also develop asthma, and approximately 66% will eventually develop allergic rhinitis.^{71,72} The skin of a person with AD is particularly susceptible to dryness. Very dry skin with impaired barrier function, places such individuals at risk for secondary bacterial, viral and fungal infections.⁷³

AD is often chronic, lasting an average of 4.4 years in children and 18.2 years in adults, though disease severity varies widely and can be influenced by external factors.⁷⁴ Individual variability can make identification of the cause(s) of a flare-up particularly difficult. Adults with AD are also predisposed to irritant contact dermatitis (when the skin becomes red and inflamed from contact with irritants such as detergent, wool, and friction with clothing).⁷⁵ Both AD and contact dermatitis cause inflammatory patches of skin. However, AD can also be aggravated by the ingestion of particular foods, spices/ flavorings or other consumables (e.g., additives, preservatives), or exposure to environmental factors such as temperature, humidity or airborne particulate matter (e.g., dust, pollen, pet dander). In contrast with irritant contact dermatitis, AD patches can occur anywhere on the skin irrespective of exposure.

AD is treated by regular application of emollients, the use of topical corticosteroids, and by minimizing exposure to known triggers. AD can occur at any age and typically manifests unpredictable exacerbations and remissions. While AD is primarily a childhood disease, onset at puberty is not uncommon. During infancy and childhood, diagnosis of AD is based on itching of the skin and rashes on the face, extremities (particularly in the bend of the elbow or knee).⁷⁶ A child's skin may improve by the age of 18 months, but the infant has a greater than normal risk of developing dry skin or hand eczema later in life. AD in teens and adults typically occurs on the hands and feet, with hand-eczema constituting 60-70% of all AD in adults. While pediatric AD may improve without treatment, adult AD is often chronic and will not resolve on its own.

Treatment of AD is aimed at hydrating the skin, reducing skin inflammation and risk of infection, alleviating itchy rashes/ patches and relieving symptoms. Medications for the treatment of AD include sedating antihistamines, immunosuppressant medication, UV therapy, topical and systemic corticosteroids, and immunomodulating agents. To soothe and soften lichenified skin (thickened skin resulting from prolonged scratching or irritation) resulting from AD, emollients may be used, whereas drying agents are applied to treat the

⁷⁰ Leung DY, Jain N, Leo HL. New concepts in the pathogenesis of atopic dermatitis. *Curr Opin Immunol* 2003;15(6):634-8.

⁷¹ Eichenfield LF, Hanifin JM, Beck LA, et al. Atopic dermatitis and asthma: parallels in the evolution of treatment. *Pediatrics* 2003; 111(3):608-616.

⁷² Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;112(6 Suppl):S118-27.

⁴² Ibid.

⁷⁴ Kiebert G, Sorensen SV, Revicki D, et al. Atopic dermatitis is associated with a decrement in health-related quality of life. *Int J Dermatol* 2002;41:151-8.

⁷⁵ Atopic dermatitis (a type of eczema) 2003.

⁷⁶ Leung DYM, Boguniewicz M, Howell MD, et al. New insights into atopic dermatitis. *The J Clin Invest* 2004;113(5):651.

“weeping” form of AD. Proper skin care practices (e.g., appropriate frequency of showering and skin moisturization) help to reduce and manage AD flare-ups.

Epidemiology

The prevalence of AD was determined by applying estimates from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) to the 2004 U.S. population. According to NIAMS, between 10 and 20 percent of all children are affected by AD, 60% of whom continue to experience symptoms of AD into adulthood. An estimated 65% of AD patients develop symptoms in the first year of life, and 90% develop symptoms before the age of five.⁷⁷ In many children, AD may resolve by age 2, and improvement by puberty (with or without treatment) is common. The crude prevalence of AD is therefore estimated to be 5,265 cases per 100,000 individuals. Applying these to the 2004 U.S. population, approximately 15.2 million individuals were estimated to experience AD.

The literature suggests that the incidence of AD has steadily increased over the past three decades. The cause of this trend is thought to be the increasing numbers of people living in cities, dry environments, or other harsh conditions where they are more likely to develop AD.

As with the other dermatitis conditions under review in this chapter, mortality from AD is quite low, with a rate of less than 0.004 per 1 million individuals per year.

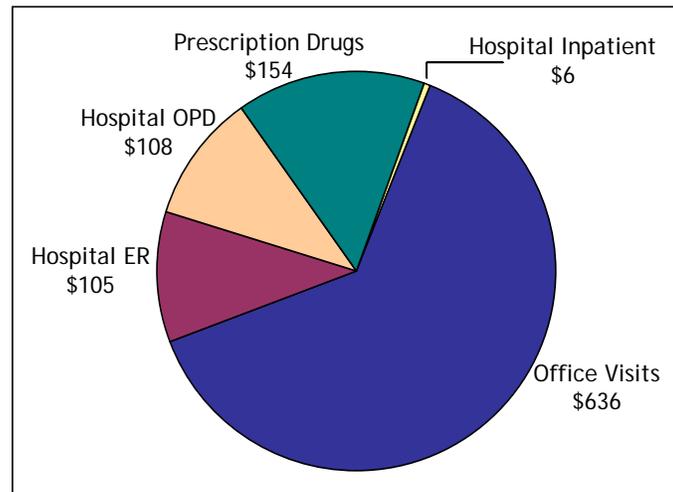
Direct Costs

The total direct cost associated with treatment for AD is over \$1 billion annually (**Figure 4.3**). As with contact dermatitis, a sizeable portion of the costs associated with AD are due to spending on prescription drugs. In 2004, prescription drugs accounted for \$154 million or 15% of total direct costs. Due to limitations in the OTC product data, OTC costs associated with this specific condition could not be specified. As with contact dermatitis, OTC products such as skin creams and lotions are frequently used to treat mild cases of AD (see Chapter 9). OTC costs for this disease are anticipated to be substantial and a leading cost category for AD.

Care for AD is provided primarily in physician offices, with more than 11 million physician office visits made due to this condition in 2004, resulting in a cost of \$636 million (**Figure 4.5**). Hospital outpatient departments were used more than 1.1 million times in 2004 for this condition, for a cost of \$108 million, and emergency rooms were used over 633,000 times for a cost of \$105 million. Hospital inpatient visits for which atopic dermatitis is listed as the primary diagnosis are relatively rare (only 2,200 in 2004), but this condition was included as a non-primary diagnosis in over 28,200 admissions. Inpatient hospital costs were responsible for \$6.2 million, less than 1% of the total direct cost of \$1 billion.

⁷⁷ Beltrani 2003.

Figure 4.3. Annual Direct Cost of Atopic Dermatitis, U.S.
(\$ millions, 2004)



Indirect Costs

From this analysis, lost productivity due to AD is estimated at \$619 million, including \$183 million in lost workdays (Figure 4.2). Since children are primarily affected by AD, the majority of productivity losses is due to caregiver lost workdays, amounting to \$249 million. The remaining \$188 million is attributable to restricted activity days due to AD. Due to the low mortality rate for AD (less than 0.004 per 1 million people per year), costs due to lost potential future earnings are virtually insignificant.

Intangible Costs Due to Quality of Life Impact

AD has been strongly linked to stress and is associated with a higher individual risk for anxiety and depressive symptoms.⁷⁸ A review of the literature indicated that stigmatization, psychological stress, lack of sleep, and adverse effects on social and financial well-being negatively affect quality of life for an AD patient.⁷⁹ AD patients have reported experiencing lower quality of life than hypertension patients, and suffer especially in the areas of vitality, social functioning, and mental health. School-aged children with AD are also at greater risk for developing psychological difficulties, which can adversely affect their academic and social development.⁸⁰ At least 60% of children with AD report that they are adversely affected by itchiness, pain, self-consciousness, and have difficulties dressing and sleeping. Some 85% of toddlers with this condition are reported to have expressed that the disease made them upset or sad.⁸¹

Of all the dermatitis conditions, AD ranks the highest in terms of diminished quality of life with a score of 12.2 on the DLQI. Willingness-to-pay is a quantitative way to measure the impact of a condition on a person's overall quality of life. In other words, the greater the willingness-to-pay, the more substantial the overall effect on quality of life. When adjusted

⁷⁸ Gupta 2003.

⁷⁹ Spengel 2003.

⁸⁰ Gupta 2003.

⁸¹ Kiebert 2002.

for disease severity and duration of illness, this score translates into an aggregate willingness-to-pay for symptom relief for all AD sufferers of more than \$2.6 billion annually.

Seborrheic Dermatitis

Seborrheic dermatitis (SD) is characterized by red patches or lesions and flaking of the skin, typically presenting on the scalp, the nose and upper lip, eyebrows, ears, and chest.⁸² Seborrheic dermatitis occurs most frequently, and is often most severe, in the winter when the climate is cold and dry.⁸³ Flaking appears as white-to-yellowish scales that may be loose, greasy or dry.⁸⁴ A common skin disorder, dandruff, is considered to be the mildest, or perhaps initial form of SD.⁸⁵

SD is neither contagious nor fatal. Factors that may increase susceptibility to the disease are genetics, stress, fatigue, weather extremes, oily skin or hair, presence of other skin disorders (such as acne), obesity and use of lotions or other agents that contain alcohol.⁸⁶ The causes of SD are unknown and vary among individuals.⁸⁷ The condition is particularly severe in individuals with HIV infection. SD may occur in conjunction with other skin diseases, such as rosacea, psoriasis, the eye irritation known as blepharitis, and acne.⁸⁸ Certain yeasts that are normal inhabitants of the skin have also been linked to the development of SD and co-morbid skin diseases, particularly in patients with immune or neurological health problems.⁸⁹

Although SD cannot be cured, management strategies aim to reduce itching, cosmetic effects (e.g., flaking) and psychosocial distress associated with the disease. While the disease may improve without intervention, SD is generally responsive to a wide variety of treatment approaches. A wide range of OTC and prescription creams, soaps and shampoos (often containing zinc or tar), and oral agents provide safe, effective, and flexible treatment options.⁹⁰ Reduction of lesions, particularly in chronic or severe cases that are unresponsive to OTC treatments, may be achieved with topical steroids and antifungal agents. However, given the chronic nature of SD and the adverse effects associated with prolonged steroid use, various combinations of prescription and OTC steroid-free alternatives may be required for adequate management of this condition.

⁸² Gupta AK, Chaudhry MM 2003.

⁸³ Gupta AK, Ryder J, Nicol K, Cooper EA. Superficial fungal infections: an update on pityriasis versicolor, seborrheic dermatitis, tinea capitis, and onychomycosis. *Clin Dermatol* 2003;21:417-25.

⁸⁴ Seborrheic dermatitis. Bethesda, MD: U.S. National Library of Medicine and National Institutes of Health, 2002. Accessed September 16, 2004. <http://www.nlm.nih.gov/medlineplus/ency/article/000963.htm>.

⁸⁵ Gupta AK, Ryder J 2003.

⁸⁶ *Ibid.*

⁸⁷ Johnson BA, Nunley JR. Treatment of seborrheic dermatitis. *Am Fam Physician* 2000; 61(9):2703-10, 2713-4.

⁸⁸ Seborrheic dermatitis 2003.

⁸⁹ Gupta AK, Bluhm R 2003.

⁹⁰ *Ibid.*

Epidemiology

A review of the literature indicates that the prevalence of SD in adults with normal immune systems is about 1-3%. It occurs most frequently in babies younger than 3 months, small children up to 3 years of age, adolescents, and young adults in their twenties.^{91,92} When SD presents in infants, it is commonly referred to as “cradle cap” and usually resolves without treatment by 8 to 12 months of age. Cradle cap can recur as adult SD at the onset of puberty. Adult SD begins most frequently around puberty, follows a waxing/waning course through adulthood, and can become more frequent after age 50.⁹³ The condition is more common in men than in women, which may be due to differences in hormone levels and amount of skin oils.⁹⁴

Individuals with compromised immune systems have a significantly higher incidence of SD, suggesting that immune system dysfunction may influence the expression of the disease. For example, incidence of SD in AIDS patients is estimated to range from 30% to 83%.⁹⁵ Patients with neurological disorders (e.g., Parkinson’s disease and multiple sclerosis) and mental disorders (e.g., depression) are also more likely to experience SD.⁹⁶

Applying prevalence rates of 1,000 to 3,000 cases per 100,000 individuals (with normal immune systems) to the 2004 U.S. population yields an estimate of between 2.9 million and 8.8 million individuals with SD. According to the CDC’s Compressed Mortality File, no deaths were reported to be attributed to seborrheic dermatitis in 2002.

Direct Costs

The total direct cost of SD is estimated to be \$179 million, excluding the cost of OTC treatment options (**Figure 4.4**). The majority of direct costs for this condition were due to physician office visits, with 953,400 visits accounting for \$58 million, or 33% of the total direct cost (**Figure 4.5**). While SD was treated infrequently in hospital emergency rooms and inpatient settings, 106,600 outpatient department visits accounted for \$10 million in costs. Hospital inpatient costs associated with SD were estimated at \$0.4 million, for 6,600 inpatient stays where SD was the primary diagnosis in 300 of those stays.

Prescription drug costs for SD were \$109 million, and were found to be substantially lower than the cost of prescription drugs for contact or atopic dermatitis (\$613 million and \$686 million respectively), due, in large part, to the lower prevalence of this disease. While data on OTC product expenditures were not available for this specific condition, the first-line treatments for many cases of seborrheic dermatitis are likely OTC products.

⁹¹ Johnson 2000.

⁹² Seborrheic dermatitis 2003.

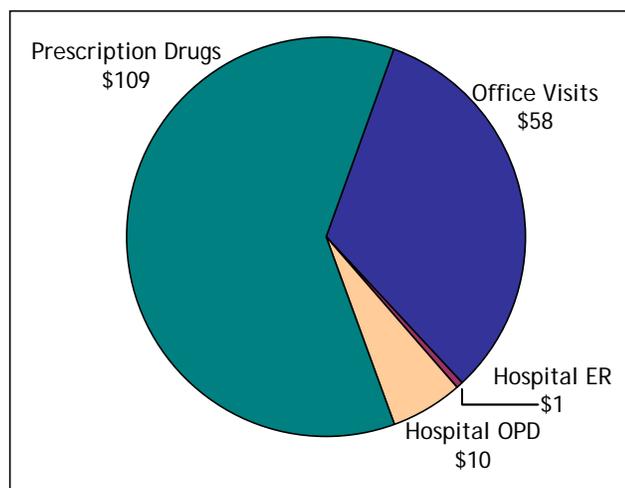
⁹³ Ibid.

⁹⁴ Johnson 2000.

⁹⁵ Gupta AK, Bluhm R, Cooper EA, et al. Seborrheic dermatitis. *Dermatol Clin* 2003;21(3): 401-12.

⁹⁶ Gupta AK, Ryder J 2003.

Figure 4.4. Annual Direct Cost of Seborrheic Dermatitis, U.S.
(\$ millions, 2004)



Indirect Costs

The indirect costs of lost productivity for SD are estimated to be \$51 million annually (Figure 4.2). Due to limitations in the epidemiological data, further delineation into lost workdays, caregiver lost workdays and restricted activity days was not feasible.

Intangible Costs Due to Quality of Life Impact

The indirect costs associated with diminished quality of life in the form of psychological distress, low self esteem, or embarrassment appear to outweigh costs of lost productivity.⁹⁷ Individuals with this condition report a mean DLQI score of 5.9 (on a scale of 0-30). Of all dermatitis conditions, quality of life impairments for individuals with SD ranked lower than the impairments associated with atopic or contact dermatitis. Willingness-to-pay is a quantitative way to measure the impact of a condition on a person's overall quality of life. In other words, the greater the willingness-to-pay, the more substantial the overall effect on quality of life. The estimated willingness-to-pay for symptom relief for individuals with SD is estimated at \$1.2 billion.

Figure 4.5. Health Care Utilization for Dermatitis

| Disease | Inpatient Hospital Stays | Inpatient Hospital Stays (primary diagnosis only) | Outpatient Hospital Visits | Emergency Room Visits | Physician Office Visits |
|-----------------------|--------------------------|------------------------------------------------------|----------------------------|-----------------------|-------------------------|
| Contact dermatitis | 59,500 | 2,500 | 933,400 | 750,600 | 10,613,100 |
| Atopic dermatitis | 28,200 | 2,200 | 1,114,000 | 633,600 | 11,350,700 |
| Seborrheic dermatitis | 6,600 | 300 | 106,600 | 6,900 | 953,400 |

Source: 2002-2003 NAMCS, NHAMCS, NHIS, NHDS adjusted to the 2004 US population

⁹⁷ Seborrheic dermatitis 2003.

Chapter 5: Microbial Skin Conditions

This chapter presents the clinical, epidemiological and economic burden of skin conditions known to be caused by microbes, predominately fungi and viruses for the three disease categories discussed below. This group includes herpes simplex and zoster, human papillomavirus, and cutaneous fungal infections.

Herpes Simplex and Zoster

Herpes simplex and herpes zoster are two categories of viruses responsible for common skin ailments such as cold sores and shingles. While herpetic infections frequently affect the skin, the virus predominantly attacks the peripheral nervous system where it may lie dormant for years in the nerve ganglia. Because of the neural involvement of these viruses, there may be associated neurological symptoms with the skin manifestations. For example, many patients with herpes simplex virus notice tingling or burning in the skin where recurrences occur. Furthermore, severe pain may precede, accompany, or follow a herpes zoster flare-up, where severe pain following resolution of skin lesions may persist for years.

Herpes Simplex

The herpes simplex viruses (HSV), referred to as HSV-1 and HSV-2, are responsible for several common and recognizable ailments such as cold sores that appear on the lips and sexually-acquired genital herpes. Among the varied presentations of HSV-1 infection, cold sores on and surrounding the lips and mouth are the most common manifestation of HSV, with approximately 20-40% of adults experiencing these outbreaks during a year. Children are most likely to experience HSV that causes lesions in and around the mouth, referred to as *gingivostomatitis* and *orolabial HSV infection*. These lesions may be extremely painful and, due to their location, may interfere with a child's ability to eat or drink, resulting in dehydration and other serious health effects.⁹⁸

Other serious manifestations of HSV-1 infections include *herpetic keratitis*, or HSV infection involving the cornea, resulting in a loss or impairment of vision. HSV is suspected of playing a role in the development of Bell's palsy, a type of temporary paralysis of the facial nerve. Another unusual manifestation of this virus is *HSV gladiatorum*, which, as the name suggests, is most commonly seen in wrestlers and other participants of high-contact sports where the virus easily spreads through direct contact with skin lesions. Other groups that are highly prone to HSV infections include clinicians, who are more likely to experience a particularly painful type of HSV infection of the fingers, referred to as *herpetic whitlow*, which may be caused by either HSV-1 or HSV-2.⁹⁹

HSV-2 is most frequently implicated in cases of *genital herpes*, though it is possible for HSV-1 to manifest in this region as well. Genital herpes is a sexually transmitted disease involving often painful blisters that form on the penis, vulva, or within the vagina. The blisters break

⁹⁸ Simmons A. Clinical manifestations and treatment considerations of herpes simplex virus infection. *J Infect Dis* 2002;15:186 Suppl 1:S71-7.

⁹⁹ *Ibid.*

to form lesions that last from 7-10 days and recur periodically, since the virus remains dormant in the nerve ganglia. Transmission of genital herpes from one person to another may occur even if the infected individual is not experiencing symptoms.

Rare complications of HSV infection may involve the internal organs, such as the brain (herpes encephalitis), or transmission of the virus from mother to fetus (neonatal herpes). Though rare, all of these complications may result in premature mortality in cases of severe infection.¹⁰⁰

There is no cure for HSV-1 or HSV-2 infection, so treatment is based on managing and shortening the frequency and duration of outbreaks. Topical antiviral drugs such as acyclovir and valacyclovir are commonly used to treat cold sores and to prevent recurrent outbreaks. Systemic antivirals may be also used for HSV-2 infections such as genital herpes and more persistent HSV-1 infections.¹⁰¹

Herpes Zoster

Herpes zoster (HZ) is caused by the varicella-zoster virus, which is also responsible for causing chicken pox. Following chicken pox, the virus retreats into the peripheral nervous system following infection, where it can lie dormant for years. If reactivated, the virus can re-emerge as herpes zoster, or “shingles,” producing an itchy or painful rash that usually follows the pattern of distribution of the affected nerve and a feeling of malaise, all of which may last for two to three weeks.¹⁰² HZ is typically managed with systemic antiviral drugs to shorten the duration of the disease, followed by pain-relieving agents and supportive therapy.

Following the initial outbreak of HZ, a serious complication known as post-herpetic neuralgia (PHN) can occur. PHN can manifest as spontaneous aching or burning, shooting pain, hypersensitivity to touch, or intense itching. By definition, PHN lasts longer than 120 days following an episode of HZ and may persist for up to ten years. Approximately 22% of those who have an episode of HZ go on to experience PHN.¹⁰³ To minimize the development of PHN, it is crucial to begin systemic antiviral therapy as soon as possible; pain management during the acute phase of HZ is also important and may involve strong pain-relieving drugs such as opioids and nerve blocks using locally injected anesthetics.

Epidemiology

Herpes Simplex

Between 60% and 95% of the world’s population is infected with one or more strains of HSV.¹⁰⁴ While the prevalence of HSV is extremely high, not all of those who carry the virus exhibit symptoms at all times and some patients may never experience symptoms. For

¹⁰⁰ Herpes simplex virus infections. The Merck Manual, 2nd ed. Accessed November 1, 2004. www.merck.com/mmhe/sec17/ch198/ch198d.html?alt=pdf.

¹⁰¹ Ibid.

¹⁰² Johnson RW, Whitton TL. Management of herpes zoster (shingles) and postherpetic neuralgia. Expert Opin Pharmacother 2004;5(3):551-9.

¹⁰³ Ibid.

¹⁰⁴ Simmons 2002.

genital herpes caused by HSV-2, females, African Americans, those who have had multiple sexual partners, and those with a history of any sexually transmitted infection are more prone to being seropositive for HSV-2.¹⁰⁵ Though HSV-1 is carried by a majority of the population, serious complications of HSV infection (of both types) are relatively rare. For example, herpes encephalitis, a herpetic infection of the brain, is extremely rare with a prevalence of 1 per million individuals per year.¹⁰⁶

The prevalence of HSV was estimated based on a study reported in the literature on the seroprevalence of HSV-1 and HSV-2. Conducted by Xu et al., this study examined data from the 1994-1998 NHANES to estimate the prevalence of HSV based on laboratory testing of serum samples. According to this study, 63% of the population carries HSV-1 and/or HSV-2.¹⁰⁷ Based on these findings, the prevalence of HSV was estimated at 56,400 per 100,000 people, making it the most prevalent skin condition under review in this study. Applying this rate to the 2004 U.S. population yields an estimate of nearly 164 million carriers of at least one strain of HSV.

Herpes Zoster

Prevalence data for HZ were not found to be reported in nationally representative databases. The overall crude incidence of HZ for all age groups is 3,400 cases per 100,000 people per year, as reported in the literature. A study based on a general practice research database found that the incidence of HZ increases with age, from 2.1 per 1,000 individuals for the population group aged <45 to 9.1 per 1,000 individuals for those older than 75.¹⁰⁸ Since HZ has an average duration of 3-4 weeks, the incidence was also assumed to be a close approximation of the prevalence, which was not found to be reported in the literature. The direct relationship between increasing age and incidence of HZ may be attributable to a waning immune system. The overall lifetime risk of developing HZ is estimated to be 20%, with only 4% of these individuals experiencing more than one episode within their lifetime.¹⁰⁹

Based on these estimates in the literature, the overall prevalence of 380 cases per 100,000 was determined. Applying this to the 2004 U.S. population yields an estimate of approximately 1.1 million individuals affected by HZ in the calendar year. There were 123 deaths attributable to HZ recorded in the 2002 Compressed Mortality File.

Direct Costs

Of the \$1.7 billion in total direct costs associated with health services for herpes simplex and zoster, prescription drug costs comprise \$1.3 billion, or 19%, reflecting over 7 million total prescriptions written in 2003, according to Scott-Levin data (**Figure 5.1**).

¹⁰⁵ Wald A. Herpes simplex virus type 2 transmission: risk factors and virus shedding. *Herpes* 2004;11 Suppl 3:130A-137A.

¹⁰⁶ Dwyer DE, Cunningham AL. 10: Herpes simplex and varicella-zoster virus infections. *Med J Aust* 2002;177(5):267-73.

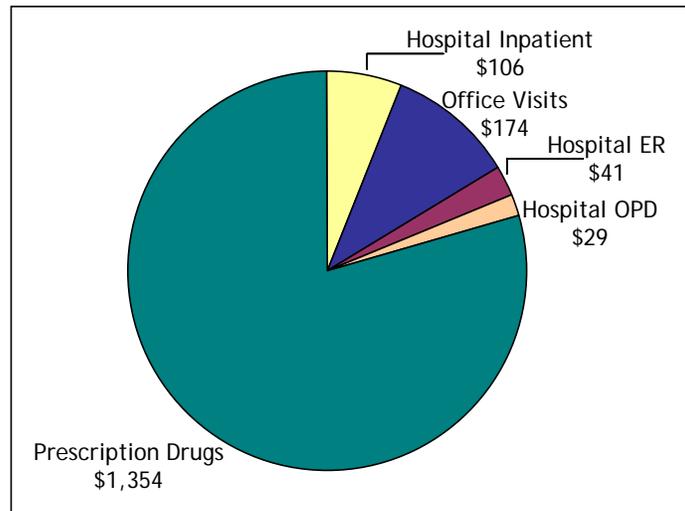
¹⁰⁷ Xu F, Schillinger JA, Sternberg MR, Johnson RE, et al. Seroprevalence and coinfection with herpes simplex virus type 1 and type 2 in the United States, 1988-1994. *J Infect Dis* 2002;185(8):1019-24.

¹⁰⁸ Opstelten W, Mauritz JW, de Wit NJ, et al. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. *Fam Pract* 2002;19(5):471-5.

¹⁰⁹ Dwyer 2002.

Direct costs associated with physician office and hospital outpatient visits totaled \$203 million, with 3.2 million visits accounting for \$174 million in physician office visits. Hospital outpatient departments were the second most frequent site of care with 316,200 visits comprising \$105.6 million (Figure 5.5). Although listed as the primary diagnosis in 28,600 inpatient hospital stays, herpes simplex or zoster were listed as a non-primary diagnosis in more than 131,600 stays. Costs associated with inpatient hospital stays for these conditions amounted to \$106 million. Costs associated with ER visits reflect only \$41 million of the total direct cost, resulting from 260,700 visits.

Figure 5.1. Annual Direct Cost of Herpes Simplex and Zoster, U.S. (\$ millions, 2004)



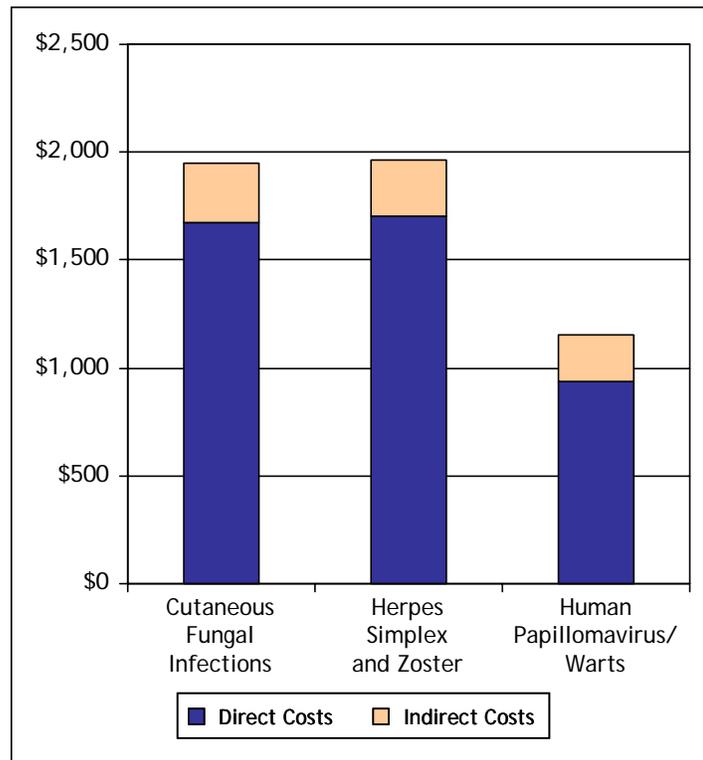
Indirect Costs

The total indirect cost associated with lost productivity for HSV and HZ was estimated at \$261 million, including \$100 million in lost workdays and \$61 million in restricted activity days for individuals who with the condition (Figure 5.2). Caregiver lost workdays accounted for \$27 million. Lost future earnings due to premature death associated with herpes zoster accounted for \$74 million of the total indirect cost.

Intangible Costs Due to Quality of Life Impact

The effects of HSV on quality of life are not well quantified, making calculation of willingness-to-pay for symptom relief impractical. In contrast, the effects of herpes zoster on quality of life are well-documented and considerable. In addition to the pain and discomfort associated with the condition itself, there are lingering effects in the form of PHN. Individuals with HZ score an average of 10.6 (on a scale of 0-30) on the DLQI. Willingness-to-pay is a quantitative way to measure the impact of a condition on a person's overall quality of life. Therefore, the greater the willingness-to-pay, the more substantial the overall effect on quality of life. When this score is applied to a willingness-to-pay perspective and adjusted for disease severity and duration, the total willingness-to-pay for symptom relief for all individuals experiencing HZ is \$7.8 million.

Figure 5.2. Annual Direct and Indirect Cost of Microbial Skin Conditions, U.S. (\$ millions, 2004)



Human Papillomavirus

Human papillomavirus (HPV) is a common virus that infects cells of the epithelium, including the epidermis of the skin and the surface layer of mucous membranes. There are more than 80 different types of HPV.¹¹⁰ HPV may remain dormant without visible symptoms in infected individuals, but it also may result in nongenital or genital warts, condylomata (wart-like growths), and polyps. While nongenital warts rarely pose a serious health problem, they can cause physical impairment and psychosocial discomfort.¹¹¹ HPV-induced lesions may become malignant, resulting in cervical cancer and other conditions.¹¹²

A wart is a benign skin tumor that develops within the skin and appears as a raised round or oval growth with a rough surface, which may be lighter or darker than the surrounding skin. The four most prevalent types of warts are common warts, plantar warts, flat warts, and genital warts. Common warts usually appear on the hands, but can occur anywhere on the skin. Plantar warts commonly appear on the soles of the feet, while flat warts are generally found on the face and neck. Genital warts are usually present in the genital region including the pubic and intertriginous areas, but can also occur inside the vagina and anal

¹¹⁰ Severson J, Evans TY, Lee P, et al. Human papillomavirus infections: epidemiology, pathogenesis, and therapy. *J Cutan Med Surg* 2001;5(1):43-60.

¹¹¹ Bellew SG, Quartarolo N, Janniger CK. Childhood warts: an update. *Cutis* 2004;73(6):379-84.

¹¹² Kuykendall-Ivy TD, Johnson SM. Evidence-based review of management of nongenital cutaneous warts. *Cutis* 2003;71(3):213-22.

canal. Non-genital warts in individuals with normal immune function are a cause of discomfort but usually resolve spontaneously within months or years.¹¹³

Warts can be transmitted by skin-to-skin contact, with varying degrees of communicability. Genital warts are especially contagious and rank as the most common sexually transmitted disease.¹¹⁴ Associated risk factors for acquiring genital warts include smoking, sexual activity with multiple partners, oral contraceptive use, pregnancy, childbearing, immune deficiency, other sexually transmitted infections, chronic inflammation, and nutritional factors.¹¹⁵ A strong correlation exists between genital warts and cancer, with a 99% prevalence of HPV in cases of cervical cancer, and 50% prevalence of HPV in cases of all other cancers of the anal and genital region.^{116,117,118}

Though no therapy is universally effective, several remedies are available for the treatment of warts, including OTC products, prescription medications, and surgery. Treatments for nongenital warts include creams containing salicylic acid, lactic acid, or imiquimod. Cryotherapy using liquid nitrogen to freeze the lesion, is another common treatment and is generally used when topical treatments are ineffective. Resistant warts can be treated with topical or systemic immunotherapy, or procedures such as intralesional bleomycin injections, surgical excision, electrosurgery, or laser surgery.

Epidemiology

Infection with nongenital HPV and warts can occur throughout life, but is relatively uncommon in infancy, more frequent in childhood, peaks during the teenage years, and sharply declines in adulthood, perhaps as the result of HPV type-specific acquired immunity.¹¹⁹ Spontaneous immunity can develop, but as many as 33% of children will have persistent HPV infection beyond two years.¹²⁰ Men and women are equally affected by nongenital warts.¹²¹

In contrast to nongenital warts, genital warts are most prevalent among sexually active adults 18-28 years of age.¹²² More than 70% of patients treated for genital warts are between 20 and 39 years of age, and 67% of treated individuals are women.¹²³ Genital warts are common, with approximately 1% of the population between the ages of 15 and 49 experiencing visible lesions.¹²⁴ At least 15% of U.S. adults have subclinical infections of

¹¹³ Gibbs S, Harvey I, Sterling JC, Stark R. Local treatments for cutaneous warts. *Cochrane Database Syst Rev* 2003;(3): CD001781.

¹¹⁴ Schiffman M, Castle PE. Human papillomavirus: epidemiology and public health. *Arch Pathol Lab Med* 2003;127(8):930-4.

¹¹⁵ Koutsky L. Epidemiology of genital human papillomavirus infection. *Am J Med* 1997;102(5A):3-8.

¹¹⁶ Likes WM, Itano J. Human papillomavirus and cervical cancer: not just a sexually transmitted disease. *Clin J Oncol Nurs* 2003;7(3):271-6.

¹¹⁷ Severson 2001.

¹¹⁸ Gall SA. Female genital warts: global trends and treatments. *Infect Dis Obstet Gynecol* 2001;9(3):149-54.

¹¹⁹ Plasencia JM. Cutaneous warts: diagnosis and treatment. *Prim Care* 2000;27(2):423-34.

¹²⁰ Koutsky 1997.

¹²¹ Fleischer AB Jr, Parrish CA, Glenn R, Feldman SR. Condylomata acuminata (genital warts): patient demographics and treating physicians. *Sex Transm Dis* 2001;28(11):643-7.

¹²² Koutsky 1997.

¹²³ Fleischer 2001.

¹²⁴ Alexander KA, Phelps WC. Recent advances in diagnosis and therapy of human papillomaviruses. *Expert Opin Investig Drugs* 2000;9(8):1753-65.

genital HPV that are invisible to the eye but detectable using HPV DNA assays, and most women who acquire genital HPV are asymptomatic.^{125,126} Most genital and nongenital HPV infections are not detectable microscopically, making detection of the virus through molecular testing the diagnostic reference standard.¹²⁷

Prevalence data for genital warts was obtained from the literature. Since most cases of HPV are asymptomatic and microscopically undetectable, seroprevalence is generally determined by molecular assay. Based on a review of the 1991 through 1994 NHANES for seroprevalence of HPV in individuals ages 12 to 59, the overall prevalence for males and females of all ages was estimated at 13% of the population. Females ages 20-29 were most likely to be seropositive for HPV, with 24.7% of this population affected.¹²⁸ Based on these estimates, the overall crude prevalence rate of HPV was determined to be 18,420 cases per 100,000 individuals. Applying this rate to the 2004 U.S. population, stratified for age, resulted in a prevalence of 58.5 million Americans seropositive for HPV.

HPV that causes cervical cancer notwithstanding (because this is not a skin manifestation of the virus), this condition is not associated with mortality. The CDC's Compressed Mortality File reported no deaths associated with HPV in 2002.

Direct Costs

The total direct cost of treatment associated with HPV and warts is \$939 million (**Figure 5.3**). The most common point of access and greatest source of costs for diagnosis and treatment of HPV and warts were physician offices, which were the site of care for nearly 5 million visits for these conditions at a cost of \$671million, or 71% of total costs. Hospital outpatient departments were the next most frequently used site of service, with 327,100 visits at \$51.8 million dollars (**Figure 5.5**).

Costs for emergency room services were lower, at \$7.5 million, with a total of 44,700 visits. There were 15,200 inpatient hospital stays associated with HPV and warts in 2002, but only 500 of these stays listed these diseases and the primary diagnosis, resulting in a cost of \$3.7 million.

Aside from the cost of care, prescription drugs for HPV and warts totaled \$205 million of the total direct cost, according to data by Scott-Levin. OTC costs were unavailable for this disease category.

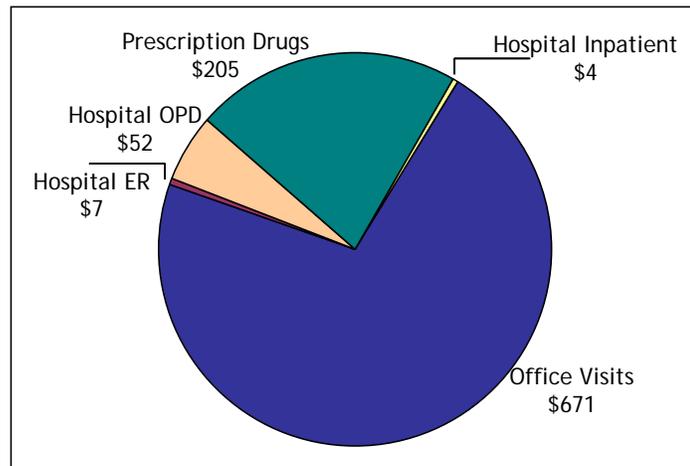
¹²⁵ Koutsky 1997.

¹²⁶ Mao C, Hughes JP, Kiviat N, et al. Clinical findings among young women with genital human papillomavirus infection. *Am J Obstet Gynecol* 2003;188(3):677-84.

¹²⁷ Schiffman 2003.

¹²⁸ Stone KM, Karem KL, Sternberg MR, McQuillan GM, et al. Seroprevalence of human papillomavirus type 16 infection in the United States. *J Infect Dis*. 2002;186(10):1396-402.

Figure 5.3. Annual Direct Cost of Human Papillomavirus, U.S.
(\$ millions, 2004)



Indirect Costs

The total indirect cost associated with lost productivity is \$214 million for these conditions (Figure 5.2). Most of this lost productivity, \$147 million, is in the form of lost workdays since most affected individuals are between the ages of 19 and 65. The remaining indirect costs of lost productivity include \$47 million in restricted activity days and \$21 million in caregiver lost workdays.

Intangible Costs Due to Quality of Life Impact

The psychological stress of having warts is often greater than the morbidity of the disease.¹²⁹ Many people find warts unsightly, especially when they occur on the hands or face, and there is considerable social stigma associated with prominent warts.¹³⁰ In a study on the psychological effects of common and plantar warts, 81% of affected individuals were moderately to extremely embarrassed by their warts, 25% said their warts made it moderately to extremely difficult to play sports, 52% experienced discomfort, and 35% reported moderate-to-severe pain associated with their warts.¹³¹ Patients with genital warts are known to suffer from shame, depression, and anxiety.¹³² A survey by the American Social Health Association revealed that more than 75% of respondents reported feelings of depression and anger, and more than 66% reported feelings of shame. Sexual enjoyment and activity are also commonly affected.¹³³

Individuals with warts have an average reported score of 4.7 (on a range of 0-30) on the DLQI. On average, individuals with this condition experience more diminished quality of life than individuals with actinic keratosis (DLQI=3.6) but less than individuals with lupus

¹²⁹ Gall 2001.

¹³⁰ Gibbs 2003.

¹³¹ Ciconte A, Campbell J, Tabrizi S, et al. Warts are not merely blemishes on the skin: a study on the morbidity associated with having viral cutaneous warts. *Australas J Dermatol* 2003;44(3):169-73.

¹³² Cox JT, Petry KU, Rylander E, Roy M. Using imiquimod for genital warts in female patients. *J Womens Health* 2004;13(3):265-71.

¹³³ Clarke P, Ebel C, Catotti DN, Stewart S. The psychosocial impact of human papillomavirus infection: implications for health care providers. *Int J STD AIDS* 1996;7(3):197-200.

erythematosus (DLQI=5.0). Willingness-to-pay is a quantitative method used to measure the impact of a condition on a person's overall quality of life. Therefore, the greater the willingness-to-pay, the more substantial the overall effect on quality of life. Viewed from a willingness-to-pay perspective, this DLQI score translates into an individual willingness-to-pay of \$425 per year for symptom relief of their condition. In the aggregate, for all individuals with HPV, this translates into a willingness-to-pay of \$2.5 billion annually.

Cutaneous Fungal Infections

Cutaneous fungal infections are among the most prevalent dermatologic conditions in the elderly and among the most commonly self-treated medical conditions.^{134,135} Fungal infections (mycoses) of the skin are most frequently caused by microorganisms called dermatophytes and yeast, though they can infrequently be caused by nondermatophyte molds.¹³⁶ Some cutaneous fungal infections, such as mycoses of the nails (i.e., tinea unguium),¹³⁷ are increasing in incidence, while others, such as tinea barbae (i.e., infection of the beard), remain rare.¹³⁸

Dermatophyte Infections

Dermatophyte infections are caused by microorganisms called dermatophytes and represent the majority of superficial fungal infections. *Trichophyton rubrum* is the most common dermatophyte in the U.S. (and the world), causing the majority of non-scalp cutaneous fungal infections.¹³⁹ Dermatophyte infections, also referred to as "tinea" infections, are classified according to the affected body site, and predominately include:

- *tinea barbae*: infection of the skin of the bearded area and neck
- *tinea capitis*: infection on skin of the scalp and head
- *tinea corporis*: infection of skin of the trunk and extremities
- *tinea cruris*: infection of the skin of the groin, proximal thigh, and buttock
- *tinea faciale*: infection of skin of the face
- *tinea manuum*: infection of skin of the palm, soles, and interdigital webs
- *tinea pedis*: (athlete's foot) infection on skin of the foot
- *tinea unguium*: (onychomycosis) infection of the nail

Transmission of tinea infections typically occurs through direct contact with infected persons, though transmission can also occur through contact with animals and soil. Moist skin provides the most favorable environment for fungi. The body responds to dermatophyte invasion by increasing skin cell production, resulting in circular lesions, scaling, and epidermal thickening.¹⁴⁰ Tinea infections can range from mild redness and

¹³⁴ Loo DS. Cutaneous fungal infections in the elderly. *Dermatol Clin* 2004;22(1):33-50.

¹³⁵ DeSimon EM, Maag P. Consult your pharmacist- common superficial fungal infections. *US Pharm* 1999;24(4).

¹³⁶ Ibid.

¹³⁷ Zuber TJ, Baddam K. Superficial fungal infections of the skin. *Postgrad Med* 2001;109(1):117-32.

¹³⁸ Vander Straten MR, Hossain MA, Ghannoum MA. Cutaneous infections dermatophytosis, onychomycosis, and tinea versicolor. *Infect Dis Clin N Am* 2003;17(1):87-112.

¹³⁹ Drake LA, Dinehart SM, Farmer ER, et al. Guidelines for care of superficial mycotic infections of the skin: tinea corporis, tinea cruris, tinea faciei, tinea manuum, and tinea pedis. *J Am Acad Dermatol* 1996;34:282-6.

¹⁴⁰ Ibid.

scaling to severe inflammation and blistering and are commonly accompanied by itching. The most prevalent cutaneous fungal infection is tinea pedis, or athlete's foot.

Cutaneous Infections Caused by Yeasts

The primary cutaneous fungal infections caused by yeast include tinea versicolor and candidiasis. Tinea versicolor is caused by the yeast known as *Malassezia furfur* and is typically located in regions of the body with greater density of sebaceous glands such as the arms, neck, and upper trunk. Additionally, facial involvement may occur in children.¹⁴¹ Tinea versicolor is characterized by scaly red to tan lesions which may be extremely itchy, and which may be hypopigmented.¹⁴² This condition is readily treatable but in susceptible individuals recurs frequently. Untreated, it can persist for several years. Recurrence rates as high as 80% after 2 years have been reported, so patients usually require preventive maintenance and periodic re-treatment.¹⁴³ Also, the condition is thought to be capable of inducing permanent discoloration of the skin, ranging from white to red to brown.

U.S. prevalence of tinea versicolor is 2-8% of the population, though the exact prevalence is difficult to calculate because many infected individuals do not seek medical attention.¹⁴⁴ Cutaneous candidiasis, which is caused by the yeast *C albicans* and other species, typically affects areas of the skin with increased moisture, such as the folds of the skin and mucous membranes (e.g., mouth, anus, perineum). Symptoms generally include cracking, redness, or maceration, as well as the presence of satellite lesions. As many as 18% of healthy people are carriers of *C albicans*, though a number of factors and disorders affecting the immune system can increase susceptibility to infection.¹⁴⁵

Early diagnosis of cutaneous fungal infections is important, as delayed recognition can lead to more extensive and difficult-to-treat infections. Diagnosis is typically performed through evaluation of patient history, followed by microscopic examination of skin cells with simple potassium hydroxide preparation. Fungal cultures may help confirm the diagnosis and are essential when considering orally administered antifungal agents.¹⁴⁶ In other cases, histological (i.e., microscopic structure of the tissue) examination may be useful in making the diagnosis. Additionally, a Wood's Light (which uses filtered UV light to examine the skin) can help in diagnosing dermatophytic skin condition.¹⁴⁷

Newer oral antifungal agents have significantly improved the efficacy and rapidity of treatment of cutaneous fungal infections. However, resistant organisms, drug associated side effects, and drug interactions require careful clinical and laboratory monitoring.¹⁴⁸ The selection of oral treatment course is based upon a number of factors, including patient age, likelihood of compliance, potential for drug interactions, and presence of other medical conditions that contraindicate treatment.¹⁴⁹

¹⁴¹ Ibid.

¹⁴² Zuber 2001.

¹⁴³ Ibid.

¹⁴⁴ Silva-Lizama E. Tinea versicolor. Int J Dermatol 1995; 34(9): 611-7.

¹⁴⁵ Ibid.

¹⁴⁶ Noble 1998.

¹⁴⁷ Weinstein 2002.

¹⁴⁸ Vander Straten 2003.

¹⁴⁹ Ibid.

Topical and/or oral antifungal agents (e.g., nystatin, azoles, itraconazole, fluconazole) are most frequently used to treat cutaneous fungal infections and duration of treatment usually lasts from a few weeks to several months.^{150,151} Additionally, combinations of antifungals with topical corticosteroids can be used with topical antifungal agents (e.g., Lotrisone)¹⁵² to provide initial symptomatic relief and to suppress inflammatory response to infection.¹⁵³ On the downside, use of corticosteroids can result in immunosuppression, so restrictions on the duration of use, patient age, and location of application may be necessary.¹⁵⁴ Certain nonspecific topical agents (e.g., selenium sulfide, propylene glycol), can also be useful in treating patients with cutaneous fungal infections.¹⁵⁵

Epidemiology

According to clinical practice guidelines from the American Academy of Dermatology (AAD), approximately 10-20% of all individuals are infected with a dermatophyte of one type or another.¹⁵⁶ Unfortunately, measures of cutaneous fungal infections in large, nationally representative datasets are not available. Due to factors such as the asymptomatic presentation of many of these conditions, coupled with the self-reporting methodology of most datasets, reliable estimates could not be derived. Applying the AAD prevalence rate of 10-20% to the 2004 U.S. population yields an estimate of between 29.3 million and 58.7 million individuals who experience at least one a cutaneous fungal infection during the calendar year.

Certain subgroups of the population are more likely to acquire particular dermatophytic infections. In general, predispositions to fungal infections of the skin include, but are not limited to, age, immunosuppression, certain neurological disorders, and other underlying diseases and treatment-related conditions.¹⁵⁷ Likewise, specific predispositions have been linked to various types of dermatophytic infections. For example, tinea corporis is most common in children (especially those exposed to infected animals), tinea cruris most often occurs in men and is also linked to obesity, and up to a third of diabetic patients may develop onychomycosis.^{158,159} Tinea pedis most frequently affects men between the ages of 20 and 40 and may affect up to 70% of adults.¹⁶⁰

The single most prevalent cutaneous fungal infection, which affects the finger and toe nails, onychomycosis represents 30% of all cases of dermatophyte infections, and the incidence is

¹⁵⁰ Weinstein 2002.

¹⁵¹ Zuber 2001.

¹⁵² Greenberg HL, Shwayder TA, Bieszk N, Fivenson DP. Clotrimazole/betamethasone dipropionate: a review of costs and complications in the treatment of common cutaneous fungal infections. *Pediatr Dermatol* 2002;19(1):78-81.

¹⁵³ Noble 1998.

¹⁵⁴ Zuber 2001.

¹⁵⁵ Drake 1996.

¹⁵⁶ Ibid.

¹⁵⁷ Vander Straten 2003.

¹⁵⁸ DeSimon 1999.

¹⁵⁹ Vander Straten 2003.

¹⁶⁰ Drake 1996.

reported to be rising due to factors such as increasing numbers of patients treated with immunosuppressive drugs and the increased lifespan of individuals.^{161,162}

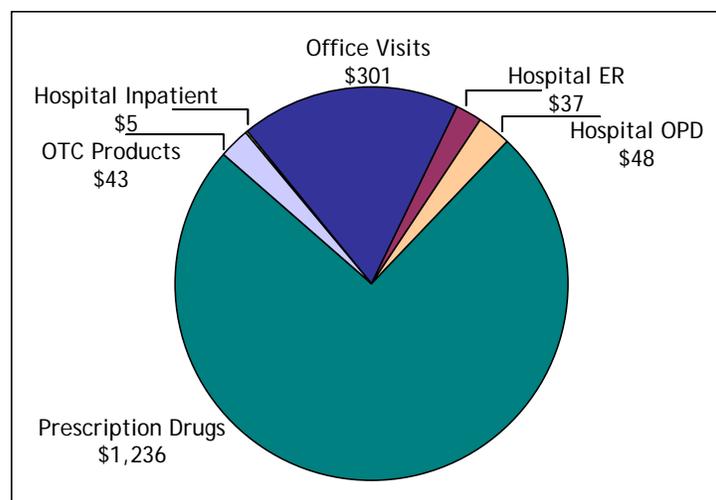
Direct Costs

Total direct costs associated with treatment of cutaneous fungal infections is approximately \$1.7 billion, with 74% of costs attributable to prescription drug products (**Figure 5.4**). Scott-Levin data indicate that 16 million prescriptions were written specifically for cutaneous fungal infections in 2004 for a total cost of \$1.2 billion. Although OTC costs are also anticipated to be high for this skin disease category, the only data available from AC Nielson that can be specifically correlated with cutaneous fungal infections is \$43 million for jock itch remedies. Costs for other applicable categories, such as special purpose skin creams, could not be accurately associated with cutaneous fungal infections because of the lack of diagnostic or procedural codes to all such associations.

Physician offices were the most frequently utilized site of care for these conditions, with nearly 4.4 million visits for cutaneous fungal infections in 2004 (**Figure 5.5**). Physician office visits accounted for \$300 million in direct costs. While only 1,600 inpatient hospital stays listed cutaneous fungal infections as the primary diagnosis, these conditions were listed as non-primary diagnoses in more than 86,000 inpatient hospital admissions, documenting the high prevalence of these conditions in the general population.

Hospital outpatient costs accounted for \$48 million of health resource utilization for this category. Emergency room costs were less extensive, estimated at \$37 million in 2004, although a sizeable proportion of these visits may be due to other health circumstances, where the fungal infection was identified as a secondary or tertiary diagnosis at the time of the visit or when patients access the ER as a primary site of care.

Figure 5.4. Annual Direct Cost of Cutaneous Fungal Infections, U.S.
(\$ millions, 2004)



*OTC costs are only for a specific type of cutaneous fungal infection, jock itch

¹⁶¹ Faergemann J, Baran R. Epidemiology, clinical presentation and diagnosis of onychomycosis. *Br J Dermatol* 2003;149(Suppl. 65):1-4.

¹⁶² Vander Straten MR, Hossain MA, Ghannoum MA. Cutaneous infections dermatophytosis, onychomycosis, and tinea versicolor. *Infect Dis Clin N Am* 2003;17(1):87-112.

Indirect Costs

The indirect costs associated with lost productivity due to cutaneous fungal infections are estimated at \$282 million annually (**Figure 5.2**). Due to the lack of information concerning age-specific prevalence, further delineation into lost workdays, caregiver lost workdays, and restricted activity days was not feasible.

Intangible Costs Due to Quality of Life Impact

Because fungal remnants can last from months to years, cutaneous fungal infections often result in reduced quality of life and increased likelihood of the spread of infection for patients. Dermatophytic infections affect patient quality of life, as considerable pain, itching, and/or other symptoms generally occur with infection. The average score on the DLQI for individuals with cutaneous fungal infections is a 5.5 (on a scale of 0-30). When adjusted for duration of illness, this DLQI score resulted in an individual willingness-to-pay of \$194 per year of symptom relief. When adjusted for disease severity and applied to all individuals with cutaneous fungal infections, the collective willingness-to-pay ranged from \$453 million to \$906 million per year.

Figure 5.5. Health Care Utilization for Microbial Skin Conditions

| Disease | Inpatient Hospital Stays | Inpatient Hospital Stays (<i>primary diagnosis only</i>) | Outpatient Hospital Visits | Emergency Room Visits | Physician Office Visits |
|-----------------------------|--------------------------|---------------------------------------------------------------|----------------------------|-----------------------|-------------------------|
| Herpes zoster and simplex | 131,600 | 28,600 | 316,200 | 260,700 | 3,245,300 |
| Human papillomavirus | 15,200 | 500 | 327,100 | 44,700 | 4,984,200 |
| Cutaneous fungal infections | 86,600 | 1,600 | 478,700 | 229,800 | 4,392,600 |

Source: 2002-2003 NAMCS, NHAMCS, NHIS, NHDS adjusted to the 2004 US population

Chapter 6: Chronic Conditions of Skin Appearance

This chapter presents estimates of the clinical, epidemiological, and economic burden of several chronic conditions of the appearance of the skin. While generally not life threatening, these conditions may cause significant psychological distress. The conditions included in this chapter are acne, vitiligo, rosacea, and hair/nail disorders.

Acne

Acne vulgaris is a common skin disease, affecting an estimated 45 million people in the U.S.^{163,164} The onset of acne typically occurs at puberty, when many physiological changes (e.g., hormone-level changes) take place in the body. With acne, excessive amounts of oil cause pores to become plugged with a combination of oil and dead skin cells. The results include red inflammation of the skin and a combination of lesions that may differ in each individual.

Acne lesions range from blackheads and whiteheads to papules, nodules, pustules, and cysts. Whereas a papule typically presents as a small, solid lesion, a nodule is often larger, solid, and inflamed. A nodule may also be painful and cause skin damage that results in scarring. Pustules and cysts are sac-like lesions that contain pus consisting of white blood cells, dead skin cells, and bacteria. Cysts also often involve significant inflammation and may evolve from a papular or nodular lesion.^{165,166} The combination and presence of acne lesions differ among patients, ranging from mild to severe and disfiguring.

Cystic acne, a more severe form of acne, can be difficult to distinguish from acne vulgaris, since cysts can occur with other types of lesions. Cystic lesions extend into deeper layers of the skin and may cause tissue destruction and subsequent scarring. Cysts may be very painful and often present as inflamed nodules.

Heredity, stress, and diet are all probable factors influencing the development and severity of acne. Acne can be managed by a variety of prescription medications (e.g., topical or oral antibiotics, and oral contraceptives for women) or OTC treatments (e.g., salicylic acid, benzoyl peroxide, and vitamin A). Treatments generally work by reducing oil production, countering blockage of the pores, and/or inhibiting the growth of acne-related bacteria. Acne medications are administered either topically as a cream or ointment or taken orally. Common treatment regimens include the combination of topical antibiotics and retinoids (derivatives of vitamin A such as tretinoin, adapalene, and tazarotene), oral antibiotics, and oral contraceptives that regulate hormones in women.¹⁶⁷ However, many medications are only effective during the course of treatment and must be used continuously to reduce or prevent flare-ups. Oral isotretinoin (Accutane™) is the one remedy that can improve acne

¹⁶³ Lee DJ, Van Dyke GS, Kim J. Update on pathogenesis and treatment of acne. *Curr Opin Pediatr* 2003;15(4):405-10.

¹⁶⁴ Lehmann H, Robinson KA, Andrews JS, et al. Acne therapy: a methodologic review. *J Am Acad Dermatol* 2002;47:231-40.

¹⁶⁵ Garner SE, Eady EA, Popescu C, et al. Minocycline for acne vulgaris: efficacy and safety. *Cochrane Database Syst Rev* 2003;(1):CD002086.

¹⁶⁶ Haider A, Shaw JC. Treatment of acne vulgaris. *JAMA* 2004;292(6):726-35.

¹⁶⁷ Thiboutot D. Acne: 1991-2001. *J Am Acad Dermatol* 2002;47:109-17.

without requiring continuous treatment to maintain the results.^{168,169} However, isotretinoin is also a teratogen that can cause fetal abnormalities.¹⁷⁰ Since response to treatment can vary considerably, individualized treatment often yields the best results.¹⁷¹

The repair of acne scars is also an important component of treatment. Acne scarring can occur as a result of damage to the skin during the healing of active acne.¹⁷² Damage causing a loss of skin tissue (collagen) results in indentations or deep cavities in the skin, while damage causing a build-up in skin tissue results in raised scars.¹⁷³ Small areas of acne scarring can be managed by injecting steroids, surgical excisions, or filling cavities with fat, collagen, or grafted skin. Larger areas of scarring require resurfacing that smoothes out the upper layers of the skin, thus removing scars and promoting the regeneration of healthy skin. Chemical peels and dermabrasions, that have been standard procedures for resurfacing, are now giving way to gentler laser resurfacing procedures.¹⁷⁴

Epidemiology

The 1996 NHIS included a question concerning self-reported “trouble with acne.” When applied to the 2003 U.S. population, responses to this question indicate a prevalence of only 5.4 million individuals. This prevalence was substantially lower than reports in the literature as well as in a systematic review performed by the Agency for Healthcare Research and Quality (AHRQ); therefore, estimates used here are based on published prevalence rates.

A review of the literature indicated that acne vulgaris is the most common skin disease of adolescence, with approximately 85% of U.S. teenagers experiencing this condition each year.¹⁷⁵ The disease may occur as early as age 8 and persist until approximately age 72, but, on average, acne affects individuals from 15 to 42 years of age.¹⁷⁶ Close to 100% of children between 12 and 17 will experience at least mild acne, regardless of heredity, ethnicity or environmental factors. Acne may resolve spontaneously by the early 20s, but, for many, the condition can be difficult to treat and persist beyond adolescence.¹⁷⁷ These considerations were used to estimate a prevalence rate of 17,600 cases of acne per 100,000 individuals. This rate, when applied to the 2004 U.S. population, indicates that 50 million individuals experience acne in a year time frame. This estimate is similar to the AHRQ estimate of 45 million individuals in 2001.¹⁷⁸

¹⁶⁸ Garner 2003.

¹⁶⁹ Meadows M. The power of Accutane: the benefits and risks of a breakthrough acne drug. FDA Consumer Magazine 2001. Accessed October 20, 2004. http://www.fda.gov/fdac/features/2001/201_acne.html.

¹⁷⁰ Stern RS. Medication and medical service utilization for acne 1995-1998. J Am Acad Dermatol 2000;43(6):1042-8.

¹⁷¹ Ibid.

¹⁷² Jordan RE, Cummins CL, Burls AJE, Seukeran DC. Laser resurfacing for facial acne scars. Cochrane Database Syst Rev 2000;(3): CD001866.

¹⁷³ Ibid.

¹⁷⁴ Hirsch RJ, Lewis AB. Treatment of acne scarring. Semin Cutan Med Surg 2001;20(3):190-8.

¹⁷⁵ Management of Acne. Summary, Evidence Report/Technology Assessment: Number 17. AHRQ Publication No. 01-E018, March 2001. Agency for Healthcare Research and Quality, Rockville, MD. Accessed November 1, 2004. <http://www.ahrq.gov/clinic/epcsums/acnesum.htm>.

¹⁷⁶ Lehmann 2002.

¹⁷⁷ Garner 2003.

¹⁷⁸ Management of Acne 2001.

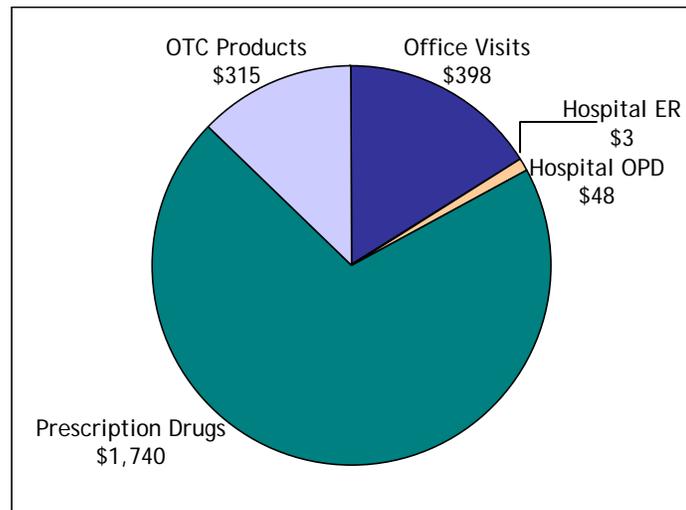
According to the Compressed Mortality File from the CDC, no deaths were attributable to acne in 2002.

Direct Costs

The total direct costs associated with the treatment of acne exceed \$2.5 billion including substantial costs for prescription and OTC products (**Figure 6.1**). Data from Scott-Levin indicated that over 11 million prescriptions were written specifically for acne in 2004 for a total cost of \$1.7 billion. According to data from AC Nielsen, Americans spend \$312 million on OTC products for acne annually, bringing the total cost for prescription and OTC products to over \$2 billion or 83% of total direct costs.

In addition to the cost of treatment, health care services account for \$430 million. According to data from NAMCS and NHAMCS, care for acne is typically sought in physician offices, with over 6.7 million visits paid to this setting in 2004, accounting for \$398 of the total cost (**Figure 6.7**). The literature reports that there are substantial differences in treatment use between sexes. A study of medical service use for acne for the years 1995-1998 found that women are 80% more likely to seek the professional care of a physician for their acne than men.¹⁷⁹ Hospital outpatient departments and emergency rooms are infrequently used for care for acne. Only 298,800 visits for acne were made to hospital outpatient departments, resulting in a cost of \$30 million. Acne is virtually never listed as the primary diagnosis for inpatient hospital stays, and was only included as a secondary diagnosis in 10,500 stays, accounting for a virtually negligible cost of \$0.1 million.

Figure 6.1. Annual Direct Cost of Acne, U.S.
(\$ millions, 2004)



Indirect Costs

The total indirect costs for acne due to lost productivity are approximately \$619 million annually (**Figure 6.2**). Since acne affects adolescents disproportionately, the amount of lost productivity for caregivers (i.e., parents taking their children to medical appointments) is substantial for this condition at \$157 million, nearly one-half of the \$307 million of lost

¹⁷⁹ Stern RS 2000.

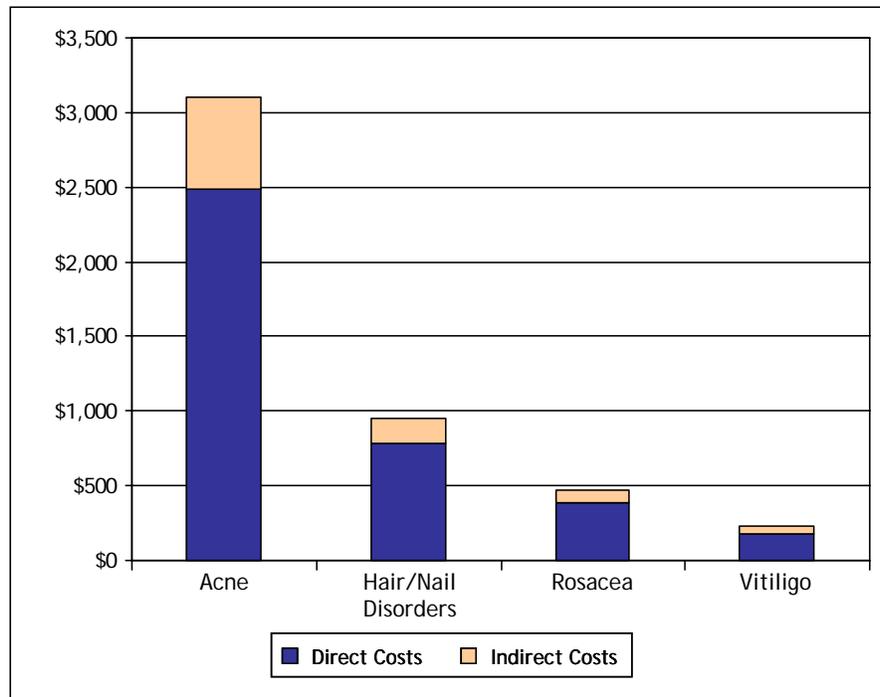
workdays for individuals with the condition. Productivity losses due to restricted activity days amounted to \$154 million. Due to the null mortality rate for acne, no indirect costs are attributable to lost future earnings resulting from premature death.

Intangible Costs Due to Quality of Life Impact

The effects of acne on quality of life are considerable, with acne patients reporting an average DLQI score of 11.9 (on a scale of 0-30). Individuals with acne consider their condition to be more detrimental to their quality of life than individuals with psoriasis (DLQI=8.8). The psychosocial effects of acne, including depression and anxiety, are well documented. A recent review reported that 25% of acne patients suffer from anxiety and 13% exhibit depression that ranges from mild to severe.¹⁸⁰

To describe the effects of this condition in a monetary context, a willingness to pay approach was adopted, whereby the quality of life effects of a particular condition are quantified to indicate how much individuals with the condition are willing to pay for symptom relief. In other words, the greater the willingness to pay, the more substantial the effects of the condition on quality of life. Based on a willingness-to-pay perspective, acne patients are willing to pay approximately \$4.00 per day to alleviate the symptoms of their condition. In the aggregate, this translates into a willingness-to-pay of \$12 billion for all individuals with acne per year.

Figure 6.2. Annual Direct and Indirect Cost of Chronic Conditions of Skin Appearance, U.S. (\$ millions, 2004)



¹⁸⁰ Haider 2004.

Vitiligo

Vitiligo appears as white patches on the skin, some of which can be quite large and may appear on any skin surface including the face, extremities, chest, and back. The severity of vitiligo can vary substantially from one or two small unpigmented lesions to the majority of the skin surface lacking pigment. With vitiligo, pigment cells normally found in the skin disappear for reasons that are not completely understood, resulting in white, pigment-free patches. Genetic factors, toxic metabolites, autoimmune response, and environmental exposures to plant, chemical or other compounds may all play a role in the development of the disease.¹⁸¹ Individuals with vitiligo are at an increased risk for developing skin cancer due to a greater propensity for sunburn and they are also at a heightened risk of developing other non-dermatological conditions such as pernicious anemia, hyperthyroidism or autoimmune disorders such as Addison's disease, Grave's disease and diabetes mellitus.¹⁸²

Vitiligo is considered to be a cosmetic condition by many health insurers, resulting in denial of coverage for treatment because the disease does not fit conventional medical necessity criteria.¹⁸³ The effects of this disease however, reach beyond the fields of cosmetic and dermatological considerations. People who suffer from vitiligo have reported feeling embarrassed, anxious, depressed or socially isolated because of their appearance. The psychosocial effects of this disorder are considered to be especially detrimental in children and teenagers. Nearly 75% of vitiligo patients consider their appearance to be moderately or severely intolerable.¹⁸⁴ Vitiligo can lead to financial losses not only because of the time required to pursue treatment, but also because a variation in physical appearance (particularly on the face, head, neck, and limbs) can lessen the likelihood of getting a job following an interview or limit career options.¹⁸⁵

Treatment options for vitiligo vary considerably and may include topical immunomodulators, ultraviolet radiation therapy, pigment cell transplant, and corticosteroids. In cases of severe vitiligo (where most of the skin surface lacks pigment), depigmentation of the remaining skin may be a more plausible treatment approach.¹⁸⁶ Other means of managing vitiligo include application of topical camouflaging agents or judicious use of sunscreen to prevent darkening of surrounding skin.¹⁸⁷

Epidemiology

There are no nationally representative datasets that include prevalence data on vitiligo. Therefore, the prevalence of vitiligo was estimated based on the peer-reviewed literature. A range of prevalence statistics was found, approximating the prevalence of vitiligo between 0.5% and 4%.^{188,189} However, literature reporting on the prevalence of vitiligo were not

¹⁸¹ Westerhof W. Vitiligo management update. *Skin Therapy Lett* 2000;5(6):1-2,5.

¹⁸² Kemp EH, Waterman EA, Weetman AP. Immunological pathomechanisms in vitiligo. *Expert Rev Mol Med* 2001;2001:1-22.

¹⁸³ Westerhof 2000.

¹⁸⁴ Parsad D, Dogra S, Kanwar AJ. Quality of life in patients with vitiligo. *Health Qual Life Outcomes* 2003;1(1):58.

¹⁸⁵ Ibid.

¹⁸⁶ Njoo MD, Westerhof W. Vitiligo: pathogenesis and treatment. *Am J Clin Dermatol* 2001;2(3):167-81.

¹⁸⁷ Westerhof 2000.

¹⁸⁸ Njoo 2001.

population based nor methodologically sound enough to derive a single, reliable prevalence rate for this study.

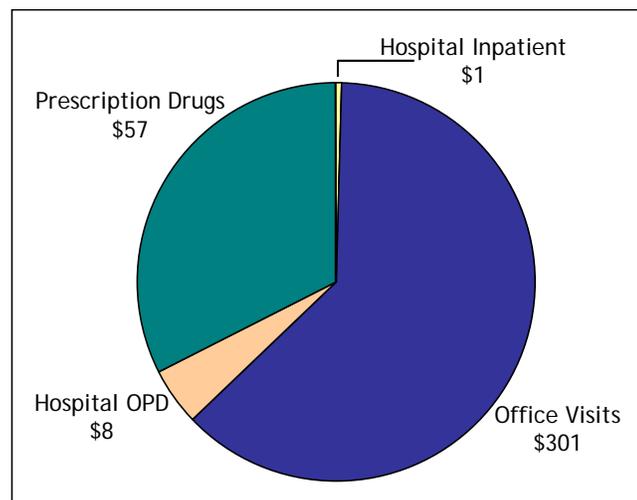
The range of prevalence statistics indicate that between 500 and 4,000 individuals per 100,000 have this condition. When applied to the 2004 U.S. population, this range indicates that between 1.4 million and 11.7 million people are affected by this condition during a calendar year. There does not appear to be any variation in prevalence across gender or racial groups. Vitiligo is not fatal, as evidenced by the fact that the CDC reported no deaths due to this condition in 2002.

Direct Costs

The total direct cost associated with treatment of vitiligo is \$175 million annually (**Figure 6.3**). The majority of this cost (62%) is attributable to physician office visits, with nearly 1.5 million visits to this site of care in 2004 (**Figure 6.7**). Hospital outpatient departments were the second most frequently used site of care, with over 54,000 visits, accounting for \$7.9 million of the total cost. Vitiligo was only listed as a primary diagnosis in 100 inpatient hospital stays for an attributable cost of \$0.6 million, but was listed as a non-primary diagnosis in more than 9,700 inpatient stays.

Prescription drugs accounted for \$56.9 million, according to Scott-Levin data, emphasizing that vitiligo is a primarily addressed through pharmacological means. Comprehensive OTC costs were not available for vitiligo, though some portion of the \$31 million spent on OTC skin bleaching products may have been used for this condition. Since these costs could not be definitively attributed to vitiligo, they are discussed in Chapter 9.

Figure 6.3. Annual Direct Cost of Vitiligo, U.S.
(\$ millions, 2004)



Indirect Costs

The annual indirect costs associated with lost productivity due to vitiligo amount to \$55 million, including \$39 million for lost workdays of individuals with vitiligo, \$6 million in caregiver lost workdays, and \$11 million in losses due to restricted activity days (**Figure 6.2**).

Intangible Costs Due to Quality of Life Impact

Vitiligo does not generate indirect costs in the form of forgone future earnings due to its nonexistent mortality rate, but it does affect quality of life for those with the condition. The average reported DLQI score for vitiligo is 5.6 (on a scale of 0-30). Studies of quality of life in vitiligo patients, have reported a range of DLQI scores from 4.8-15, suggesting that the effects of this disease may be exacerbated by factors such as the degree of body surface area affected or individual patient characteristics. For example, while there does not appear to be an increased prevalence based on ethnicity, darker skinned individuals have reported more severe reductions in quality of life because the white patches are more contrasted against darkened skin tones. Furthermore, although males and females are equally affected, females tend to report greater reductions in quality of life due to vitiligo.

Willingness-to-pay is a quantitative way to measure the impact of a condition on a person's overall quality of life. In other words, the greater the willingness-to-pay, the more substantial the overall effect on quality of life. When the DLQI score for vitiligo is considered from a willingness-to-pay perspective, individuals with this condition are willing-to-pay an average of \$2.80 per day to alleviate the symptoms of their condition. When the chronic nature of this disease is taken into account, this amounts to \$1,014 per year for each vitiligo patient. Collectively, the willingness to pay for all vitiligo patients for symptom relief is \$63 million per year.

Rosacea

Rosacea is a common skin condition identified by frequent flushing and redness of the face, known as facial erythema. Facial erythema, the primary symptom of rosacea, may affect the forehead, nose, cheeks, and chin. It is also frequently accompanied by a burning sensation of the skin and slight swelling of the face.¹⁹⁰ Other main identifiers of rosacea include the papules (i.e. small and solid lesions that appear as pink bumps) and pustules (small sac-like lesions containing pus) and telangiectasia (visible blood vessels on the face).^{191,192} Several secondary features of rosacea include eye inflammation and sensitivity, watery and/or bloodshot eyes, skin sensitivity to light, thickening of the skin on the forehead, chin, and cheeks, dryness of the skin, itchiness and/or stinging sensations, and swelling that can result in a red and bulbous nose.

¹⁹⁰ Del Rosso JQ. Medical treatment of rosacea with emphasis on topical therapies. *Expert Opin Pharmacother* 2004;5(1):5-13.

¹⁹¹ Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol* 2004;51(3):327-41.

¹⁹² Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol* 2002;46:584-7.

The causes of rosacea are unknown, though abnormalities in the small blood vessels beneath the skin are thought to play a key role, and are likely to be the cause of flushing and telangiectasia. Other theories involve environmental factors, microorganisms, gastrointestinal tract diseases, and degeneration of the skin and immune system. Behavioral factors such as excess exposure to heat and sunlight and consumption of alcoholic beverages, spicy foods, and hot drinks (especially coffee and tea) may also be factors that prompt or exacerbate rosacea flare-ups.¹⁹³ However, as with many skin diseases, the triggers of rosacea flare-ups can vary significantly, necessitating individualized and flexible treatment strategies and strong communication between the clinician and patient.

Rosacea often involves periods of exacerbation and relative remission throughout a patient's life. Though the condition is not curable, long-term management can reduce papule and pustule lesions, decrease intensity of erythema, and minimize the number and intensity of flare ups. Proper skin care, involving the use of non-medicated and/or hypoallergenic cleansers and moisturizers and protection from the sun, is considered essential in any rosacea management regimen. Treatments for rosacea include oral and topical therapies, such as antibiotics, and steroid drops for the eyes. Prescription gels, creams, and cleansers are also used and usually contain sulfacetamide, sulfur, azelaic acid, clindamycin, benzoyl peroxide, or topical erythromycin.¹⁹⁴ More severe or persistent cases of inflammatory rosacea involving acne might also be treated with oral isotretinoin.¹⁹⁵

Exacerbation of the rosacea flush can be minimized by avoiding potential triggers such as hot liquids, alcohol, spicy foods, and some cosmetics. Avoidance of sunlight, the most common trigger of flare-ups, is especially important for a rosacea patient because UV light induces alteration and degradation of already sensitive skin. When telangiectasia and redness become permanent, laser surgery and electrosurgery may help reduce the visibility of blood vessels and remove the unwanted tissue buildup around the nose.

Epidemiology

Data on rosacea is not captured in the nationally representative datasets reviewed for this study. Therefore, prevalence estimates were made based on statistics reported by NIAMS. According to 2002 estimates from NIAMS, rosacea affected more than 14 million individuals, 60% of whom are diagnosed before age 50.^{196,197} The literature indicates that rosacea is more prevalent in women than men, but that severe rosacea is most often experienced by men.¹⁹⁸ This condition occurs in people of all skin colors, but most commonly affects Caucasians (particularly those with Celtic or Scandinavian heritage).¹⁹⁹

These considerations were used in deriving estimates of the prevalence rate of 5,000 cases of rosacea per 100,000 individuals. When applied to the 2004 U.S. population, an estimated

¹⁹³ van Zuuren EJ, Graber MA, Hollis S, et al. Interventions for rosacea. *Cochrane Database Syst Rev* 2004;(1):CD003262.

¹⁹⁴ Del Rosso 2004.

¹⁹⁵ van Zuuren 2004.

¹⁹⁶ Health topics: questions and answers about rosacea. Bethesda, MD: National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2002. Accessed September 15, 2004.

¹⁹⁷ Del Rosso 2004.

¹⁹⁸ van Zuuren 2004.

¹⁹⁹ Gupta 2003.

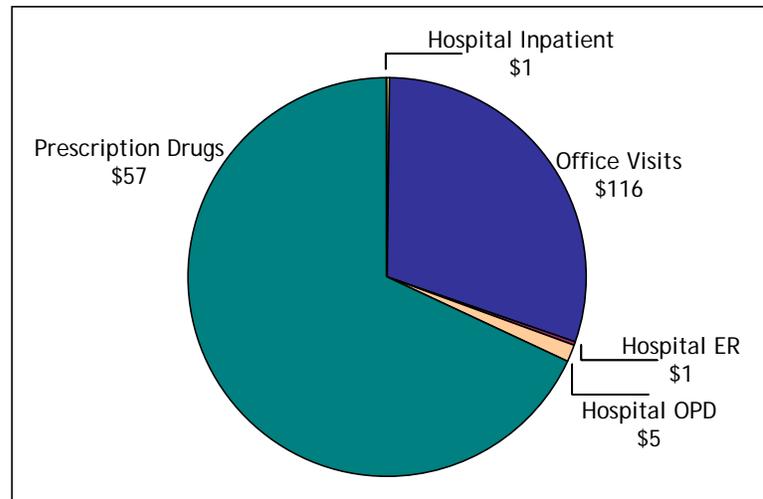
14.7 million individuals were affected by rosacea in the calendar year. Rosacea is not a condition associated with mortality, as no deaths were reported by the CDC in 2002.

Direct Costs

The total direct cost associated with the treatment of rosacea is \$385 million (**Figure 6.4**). According to data from NAMCS, Americans made more than 1.8 million visits to physician offices for treatment of rosacea in 2004. Hospital outpatient departments and emergency rooms were only used in 47,700 cases, and rosacea was listed as a primary diagnosis in only 100 hospital admissions (**Figure 6.7**). Of the \$122 million spent on health care services in outpatient settings for rosacea, 95% was directed towards services provided in physician offices.

There were 2.2 million prescriptions written for treatment of rosacea in 2004, costing a total of \$262 million, according to Scott-Levin data. Prescription drugs account for the largest share of the direct costs associated with rosacea, comprising 68% of the total direct costs of treatment.

Figure 6.4. Annual Direct Cost of Rosacea, U.S.
(\$ millions, 2004)



Indirect Costs

Annual indirect costs associated with lost productivity due to rosacea amount to \$80 million, including \$36 million for lost workdays, \$19 million in caregiver lost workdays, and \$26 million in losses due to restricted activity days (**Figure 6.2**). Since rosacea has a null mortality rate, it does not generate indirect costs in the form of lost future earnings.

Intangible Costs Due to Quality of Life Impact

The quality of life implications for individuals with rosacea are considerable. The average DLQI score for individuals with this condition is 6.7 (on a scale of 0-30). To put this score in perspective, on average, those with rosacea indicate a greater reduction in quality of life due to their condition than individuals who have vitiligo (DLQI=5.6). Willingness-to-pay is a

quantitative way to measure the impact of a condition on a person's overall quality of life. In other words, the greater the willingness-to-pay, the more substantial the overall effect on quality of life.

The average willingness-to-pay for individuals with rosacea for symptom relief is \$2.80 per symptomatic day. When extrapolated to the entire population of rosacea patients, the aggregate willingness-to-pay is \$1.6 billion per year.

Hair and Nail Disorders

This section includes evaluation of the clinical and economic burden associated with hair and nail disorders. Each category includes multiple disorders.

Hair Disorders

Hair disorders consist of several conditions and involve hair loss, excessive hair growth or distribution, and infection of the hair follicles. While most hair disorders are not life threatening, they present important cosmetic concerns for patients and may result in significant psychosocial distress. Many hair disorders can be warning signs of more severe underlying health conditions, such as diabetes, thyroid disease, arthritis, or Addison's disease.

Alopecia, or hair loss, can develop suddenly or gradually as the result of various factors. It is typically caused by a shortening of the hair growth cycle, to the point where there is no growth at all.²⁰⁰ Alopecia generally occurs in the scalp and face and can be patchy or extensive, potentially leading to total loss of scalp and/or body hair. Alopecia may be due a number of factors including physical or psychological stress, changing hormonal levels due to advancing age, trauma and resulting scars, and physical or psychological stress. Perhaps the most recognizable form of alopecia is the commonly called "male pattern baldness." Numerous factors are associated with alopecia, including but not limited to genetic predisposition, malfunctions in the immune system, and certain medical conditions, such as eating disorders, thyroid disease, lupus erythematosus, and hormonal imbalances.²⁰¹ While alopecia usually affects adults, hair loss can begin at any age. Alopecia areata causes the loss of clumps of hair, oftentimes in individuals younger than the age of 20.

In contrast to alopecia, hirsutism is characterized by excessive hair growth. Especially of concern for many women, hair can become extremely dark and thick, with growth anywhere on the body though most often on the face, back, chest, and abdomen.

Inflammation of the hair follicles, known as folliculitis, can occur anywhere on the skin or scalp, and is often exacerbated by physical or chemical irritation. The condition, often caused by *Staphylococcus* bacteria, usually presents as gradually evolving red bumps that may be accompanied by itching and soreness. Sometimes, hair follicles of the beard curl inwards and puncture the skin, resulting in infection and inflammation.

²⁰⁰ Drake LA, Ceilley RI, Cornelison RL, et al. Guidelines of care for alopecia areata. *J Am Acad Dermatol* 1992;26,2:247-50.

²⁰¹ *Ibid.*

Hair disorders are often clinically apparent upon physical examination, though subsequent diagnostic tests are required in some circumstances to determine their cause. Because hair disorders accompany many other medical conditions, immune, endocrine, hormone level, and/or other laboratory analyses may be performed to rule in or rule out other underlying diseases that contribute to the condition (e.g., thyroid disease and other endocrine disorders, systemic disease, or severe infection).²⁰²

Most treatments for hair disorders only occur when individuals express concern over their appearance. Several treatment options exist for hair loss, and treatment success often depends upon the age at disease onset and the extent of hair loss.²⁰³ Treatment options for alopecia include topical solutions and/or oral medications, though the majority of these drugs are effective in preventing further hair loss but not necessarily re-growing previously lost hair.²⁰⁴ Another option for treatment is hair transplant surgery, in which healthy hair follicles are surgically removed from one area of the scalp and reinserted into the balding areas. Hirsutism is generally treated with oral contraceptives, androgen blockade, and/or hormonal suppression, though the visible symptoms can be temporarily alleviated through shaving and waxing, or more permanently through electrolysis or laser treatment. Treatment of folliculitis is typically achieved via oral antibiotics though topical antibiotic creams or lotions may also be used.²⁰⁵

Nail Disorders

Nail disorders include ingrown nails, onychomycosis (a fungal nail infection), paronychia (inflammation and infection of the nail), onycholysis (separating of the nail plate from the nail bed), and splinter hemorrhages (vertical lines on the nail caused by injury or drugs). Nail disorders comprise about 10% of all skin conditions, and most minor nail injuries heal without treatment.²⁰⁶ Risk factors for developing nail disorders increase significantly with age, hormone imbalance, and/or disease. The symptoms, effects and treatment of nail disorders vary considerably, depending on the type and severity of condition. Color and shape changes, swelling of the nail folds, and/or pain are frequent symptoms of nail disorders.²⁰⁷

Diagnosis of nail disorders typically occurs during clinical examination but can also involve microscopic inspection in cases where fungal infection is indicated. Additionally, a fungal culture or nail biopsy may be performed in some cases. Many nail conditions (e.g., white spots, splinter hemorrhages) naturally resolve, though treatment can be appropriate in moderate to severe cases. Treatments for nail disorders are typically either surgical or non-surgical, involving the use of topical and/or oral medications, though it is often difficult for topical medications to penetrate the nail.

²⁰² Drake 1992.

²⁰³ Ibid.

²⁰⁴ Springer K, Brown M, Stulberg DL. Common hair loss disorders. *Am Fam Physician* 2003;68:93-102.

²⁰⁵ Drake 1992.

²⁰⁶ Ibid.

²⁰⁷ Guidelines of care for nail disorders. *J Am Acad Dermatol* 1996;34:529-33.

Epidemiology

With the exception of alopecia in men, which was captured by NHANES, numbers to support prevalence estimates were unavailable from the nationally representative datasets. Therefore, prevalence rates were estimated from studies reported in the literature.

Alopecia differentially affects males and females. For alopecia in men, a follow-up to the NHANES I conducted in 2000 found that this condition is strongly correlated with age. In a review of 4,421 men ages 25-75, the prevalence of alopecia in the 25-34 age cohort was 19%, increasing to a prevalence of 63% in the 65 or older cohort.²⁰⁸ Studies of the prevalence of alopecia in women are relatively infrequent. One 2001 study found that 6% of women under the age of 50 and 38% of women over the age of 70 experience alopecia.²⁰⁹ These considerations were used in estimating the overall crude prevalence rate of 17,480 cases of alopecia per 100,000 individuals. When applied to the 2004 U.S. population, alopecia affected 13.5 million women and 36.4 million men.

Epidemiological statistics for other hair conditions are lacking in the literature and nationally representative datasets. One recent report estimated that the prevalence of hirsutism may range from 5 to 15% of American women, but due to a lack of population-based studies for this condition, an overall crude prevalence rate could not be calculated.²¹⁰ No prevalence estimates for folliculitis were available in the literature.

Nail disorders are known to disproportionately affect the elderly, due to increased susceptibility for infection, circulation problems, and/or regular use of certain medications (e.g., cancer chemotherapeutic agents, psoralens, and retinoids).^{211,212} Overall, fungal nail infections affect about 12% of all Americans.²¹³ A number of diseases, including liver, kidney, heart, lung, anemia, and diabetes, are also associated with the development of nail problems. For example, about 10-50% of patients with psoriasis and about 80% of patients with inflammatory psoriatic arthritis have nail disorders (e.g., pitting, ripping, splinter hemorrhages, discoloration, etc.). When these considerations were used to estimate the overall crude prevalence of nail conditions with the 2004 U.S. population, over 35 million individuals were affected by at least one nail condition during the calendar year.

Hair and nail disorders are seldom associated with mortality; the CDC Compressed Mortality File for 2002 reported only 4 deaths associated with these conditions.

Direct Costs

The total direct cost associated with hair and nail disorders is \$780 million (**Figure 6.6**). The majority of these costs, \$468 million, is associated with care and services provided for the conditions. The remaining costs are attributable to OTC and prescription drugs. According

²⁰⁸ Rhodes T, Girman CJ, Savin RC, Kaufman KD, et al. Prevalence of male pattern hair loss in 18-49 year old men. *Dermatol Surg*. 1998;24(12):1330-2.

²⁰⁹ Birch MP, Messenger JF, Messenger AG. Hair density, hair diameter and the prevalence of female pattern hair loss. *Br J Dermatol*. 2001;144(2):297-304.

²¹⁰ Azziz R. The evaluation and management of hirsutism. *Obstet Gynecol*. 2003;101(5 Pt 1):995-1007.

²¹¹ *Ibid.*

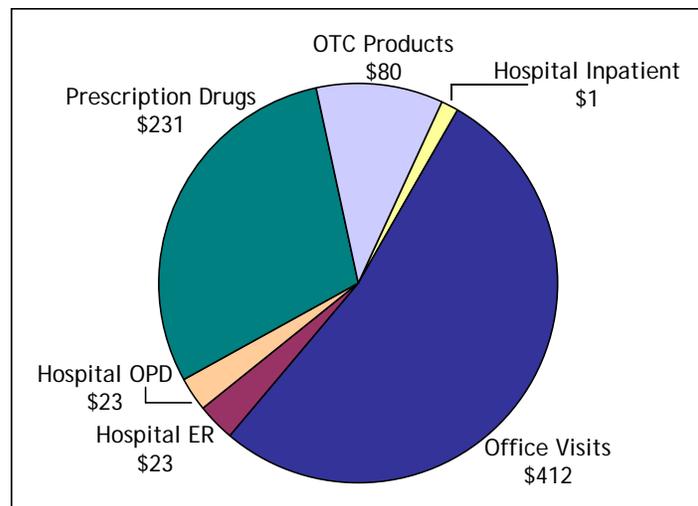
²¹² Drug-induced nail disorders: prevention is best. *Drugs & Therapy Perspectives* 2000;16(1):13-16.

²¹³ *Ibid.*

to Scott-Levin data, prescription drugs prescribed specifically for hair and nail disorders amounted to \$231 million. However, the OTC market for these conditions was responsible for \$80 million in sales for hair growth products alone, suggesting that OTC products are heavily used for these conditions.

The primary site of care for these conditions is the physician office, with approximately 3.6 million visits made to this location for a cost of \$412 million (**Figure 6.7**). Hospital outpatient visits and emergency room visits were fewer, amounting to \$46 million of the total direct cost. Hair and nail disorders were listed as the primary diagnosis in 2,800 inpatient hospital stays, and listed as a secondary diagnosis in 22,900 stays, for a total cost of \$11 million.

Figure 6.6. Annual Direct Cost of Hair and Nail Disorders, U.S.
(\$ millions, 2004)



*OTC Product costs are for hair growth products only

Indirect Costs

Indirect costs associated with lost productivity for hair and nail disorders are estimated at \$175 million annually (**Figure 6.2**). Due to the association between increasing prevalence and advancing age for these conditions, the majority of the indirect costs are attributable to lost workdays and restricted activity days for individuals who have the condition (\$86 million and \$61 million, respectively). The remaining \$28 million is attributable to lost workdays of caregivers. Because virtually no mortality is associated with hair and nail disorders, there are no costs associated with lost future earnings due to premature death.

Intangible Costs Due to Quality of Life Impact

In addition to the indirect costs of lost productivity, there are significant quality of life concerns associated with hair and nail disorders. Little is known about the effects of nail disorders on quality of life. While nail disorders can inhibit daily activities due to decreased mobility or dexterity, there have not been studies that quantify these effects into a utility or DLQI score. For hair disorders, however, several studies suggest that psychosocial issues may stem from these conditions, especially for women who have reported significant

psychosocial problems attributable to hair loss, including anxiety, depression, and decreased self-esteem.²¹⁴ On the DLQI, individuals with hair loss scored an average of 8.3. Individuals with hirsutism reported even more substantial impairment with a score of 12.8. These scores indicate that individuals with hair disorders experience impairment to their quality of life that exceeds that of cutaneous fungal infections (DLQI=5.5), rosacea (DLQI=6.7), or seborrheic dermatitis (DLQI=5.9).

Willingness-to-pay is a quantitative way to measure the impact of a condition on a person's overall quality of life. In other words, the greater the willingness-to-pay, the more substantial the overall effect on quality of life. When the effects on quality of life for individuals with alopecia are considered from a willingness-to-pay perspective, the average amount that an individual with this condition is willing to pay for symptom relief is \$1,114 annually. This amount, when applied to the entire population of individuals with alopecia and adjusted for disease severity, translates into a willingness-to-pay of \$17 billion annually.

Figure 6.7. Health Care Utilization for Chronic Conditions of Skin Complexion

| Disease | Inpatient Hospital Stays | Inpatient Hospital Stays (primary diagnosis only) | Outpatient Hospital Visits | Emergency Room Visits | Physician Office Visits |
|-------------------------|--------------------------|------------------------------------------------------|----------------------------|-----------------------|-------------------------|
| Vitiligo | 9,700 | 100 | 54,000 | 1,900 | 1,456,800 |
| Acne | 10,500 | - | 298,800 | 16,900 | 6,775,500 |
| Rosacea | 7,900 | 100 | 43,700 | 4,000 | 1,836,200 |
| Hair and nail disorders | 22,900 | 2,800 | 224,800 | 158,000 | 3,586,200 |

Source: 2002-2003 NAMCS, NHAMCS, NHIS, NHDS adjusted to the 2004 US population

²¹⁴ Poot F. [Psychological consequences of chronic hair diseases] Rev Med Brux 2004;25(4):A286-8.

Chapter 7: Skin Conditions Due to Immune System Response

This chapter examines the clinical, epidemiological, and economic burden of skin conditions that arise from the immunological responses. These conditions can be associated with immune responses to environmental stimuli or to autoimmune responses, where the body develops an immune response against itself. The conditions included in this chapter are lupus erythematosus, diseases collectively referred to as immuno-bullous diseases, and psoriasis. Other skin conditions discussed elsewhere in this report, such as atopic dermatitis and seborrheic dermatitis, may also be affected with immune system responses.

Lupus Erythematosus

Lupus erythematosus (lupus) is a frequently devastating, multisystem autoimmune disease that affects one or more vital organs, including the skin, central and peripheral nervous systems, and muscles, and involves periods of remission and relapse. Lupus can range from being a mild to life-threatening condition, can be resistant to treatment, and often results in significant patient suffering. This disease affects about 1.4 million Americans annually.²¹⁵ Skin is affected in about 70% of patients, and cutaneous involvement can precede, follow, or parallel other systemic disease activity.^{216,217} Cutaneous lupus can include potentially painful skin lesions (often ring/coin shaped or in a butterfly formation), often appearing in the upper body regions. Patients with associated systemic disease, arthritis, pleurisy, anemia, and renal diseases, among other conditions, may also be at an increased risk for developing cutaneous lupus.²¹⁸

Symptoms of lupus include, but are not limited to, photosensitivity, localized or patchy hair loss, skin lesions or pustules, itchiness, hypo- or hyperpigmentation, and mucosal ulcers near the mouth or nose. Skin lesions generally present on the scalp, face, ears, arms, and/or neck and sometimes the trunk. Patients with cutaneous lupus can have a variety of other skin conditions (e.g., blistering, wart-like projections), but cutaneous manifestations directly associated with lupus are typically of the following four main types.²¹⁹

- **Acute cutaneous lupus erythematosus (ACLE)** is the most photosensitive form of lupus, with a strong association to systemic disease. It is characterized by either localized or generalized forms, confluent redness, often with swelling, of the skin on the face (often the nose), with potential postinflammatory pigmentation changes or blistering. ACLE patients may develop systemic lupus during the course of their disease, usually with abrupt eruption.²²⁰

²¹⁵ Eliminate disparities in lupus. Atlanta, GA: Center for Disease Control and Prevention, 2004. Accessed November 1, 2004. <http://www.cdc.gov/omh/AMH/factsheets/lupus.htm>.

²¹⁶ Drake LA, Dinehart SM, Farmer ER, et al. Guidelines of care for cutaneous lupus erythematosus. *J Am Acad Dermatol* 1996;34(5 Pt 1):830-6.

²¹⁷ Patel P, Werth V. Cutaneous lupus erythematosus: a review. *Dermatol Clin* 2002;20(3):373-85.

²¹⁸ Drake 1996.

²¹⁹ Ibid.

²²⁰ Patel 2002.

- ***Discoid lupus erythematosus (DLE)*** is a chronic photosensitive dermatitis that may occur in patients with systemic disease or progress to systemic disease (5-10% go on to develop systemic lupus).²²¹ It is the most common form of cutaneous lupus, characterized by disk-shaped lesions above the neck, with potential changes in pigmentation and atrophic scarring. About 14-27% of patients have extracutaneous signs of disease.
- ***Subacute cutaneous lupus erythematosus (SCLE)*** is a photosensitive dermatitis, commonly occurring with serologic abnormalities. It is characterized by lesions on the arms, face, and neck, with potential postinflammatory depigmentation.
- ***Lupus erythematosus non-specific lesions***, for example, leukocytoclastic vasculitis, is a large and diverse group that often reflects underlying systemic disease activity.²²²

Cutaneous lupus erythematosus can mimic other skin disorders; for example, the clinical appearance of ACLE can be difficult to distinguish from certain forms of acne rosacea.²²³ Thus, careful assessment is critical to timely diagnosis. Evaluation most often includes a skin biopsy and various immunological laboratory tests, such as immunofluorescence (i.e., the use of antibodies chemically linked to a fluorescent dye to identify/measure antigens; referred to as the “lupus band test” when used in these circumstances) and antinuclear antibody (i.e., abnormal antibodies that can indicate autoimmune disease) assays. Patients should receive clinical and laboratory assessment (e.g., blood cell count, urinalysis, erythrocyte sedimentation rate, antinuclear antibodies) to identify underlying nervous system, hematological, renal, and/or cardiovascular disease that may inform treatment regimens and reduce adverse health outcomes.

Cutaneous manifestations of lupus are frequently managed in conjunction with other medical specialists, since lupus often affects multiple organ systems. Goals of cutaneous treatment are typically prevention of lesion progression and improvement in physical appearance. Precautions are often taken to avoid contributory environmental agents, such as the sun and heat. In general, topical medications can be used for treatment of the skin. Low-strength topical corticosteroid preparations (e.g., hydrocortisone, aclomethasone, desonide) can control lesions located in sensitive areas, such as the face, and mid-potency agents (e.g., fluorinated corticosteroids) are often used on the arms and trunk, while high-potency agents (e.g., clobetasol, betamethasone disproportionated, halobetasole) can be used on the palms and soles.²²⁴ Severe cutaneous lupus is most often treated with immunosuppressives (e.g., azathioprine, methotrexate, cyclophosphamide).

Epidemiology

Prevalence estimates for lupus were derived from a study of the Rochester Epidemiology Project. The study screened medical records in Rochester, Minnesota, using criteria from the American College of Rheumatology to select lupus cases. Based on this study, we estimated a sex- and age-adjusted prevalence rate of 122 cases per 100,000 individuals.

²²¹ Ibid.

²²² Drake 1996.

²²³ Ibid.

²²⁴ Drake 1996.

Applied to the 2004 U.S. population, this rate projects to 358,300 individuals with lupus erythematosus.²²⁵

Cutaneous lupus can affect people of all ages and ethnicities, though there is substantial variation in prevalence associated with gender and ethnicity. Females are affected more frequently than males with a ratio of 7:1 that increases to 11:1 during the childbearing years.²²⁶ Lupus is two-three times more common in African-Americans, Asians, Native Americans, and Hispanics.²²⁷

The mortality rate of lupus has been declining since the 1950s, when only half of individuals with this condition survived longer than four years from diagnosis. Currently, the five-year survival rate is 97% and the ten-year survival rate is an estimated 90%.²²⁸ The CDC has indicated significant disparities in death rates for lupus, including crude death rates that are five times higher for women than men, and nearly three times higher for African Americans than Caucasians.²²⁹

Direct Costs

The total direct cost associated with treatment of lupus erythematosus is \$347 million (**Figure 7.1**). Prescription drugs account for nearly half of the total direct cost, at \$159 million. Additionally, as noted above, lupus erythematosus is one of the diseases for which certain significant drug costs, (i.e., for drugs sold through specialty pharmacies), are not captured by the datasets used in this study. While physician offices were most frequently utilized, with over 1.1 million visits, the cost associated with inpatient hospital stays exceeded that of physician office visits (**Figure 7.5**). Lupus erythematosus was listed as a primary diagnosis in more than 19,000 hospital admissions, and as a secondary or supporting diagnosis in more than 136,300 admissions. The total cost associated with inpatient care was \$96 million and the costs associated with physician office visits was \$67 million.

²²⁵ Uramoto KM, Michet CJ Jr, Thumboo J, Sunku J, et al. Trends in the incidence and mortality of systemic lupus erythematosus, 1950-1992. *Arthritis Rheum* 1999 Jan;42(1):46-50.

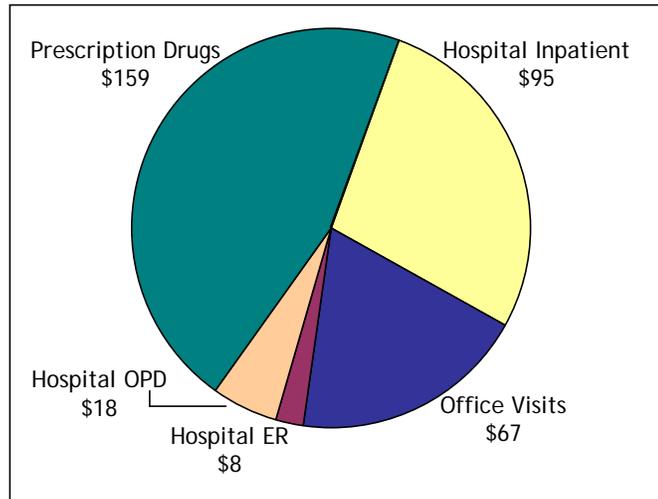
²²⁶ Manzi S. Epidemiology of systemic lupus erythematosus. *Am J Manag Care* 2001;7(16 Supple):S474-9.

²²⁷ Lupus fact sheet. Washington, DC: Lupus Foundation of America, Inc., 2001. Accessed November 1, 2004. <http://www.lupus.org/education/factsheet.html>.

²²⁸ Lawrence RC, Helmick CG, Arnett FC, Deyo RA, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998 May;41(5):778-99.

²²⁹ Trends in death from systemic lupus erythematosus: United States, 1979-1998. Atlanta, GA: Centers for Disease Control and Prevention, 2002. Accessed January 25, 2005. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5117a3.htm>.

Figure 7.1 Annual Direct Cost of Lupus Erythematosus, U.S.
(\$ millions, 2004)



Indirect Costs

The total annual indirect cost of lupus due to lost productivity is estimated at \$201 million (Figure 7.2). Due to a lack of information concerning age-specific prevalence, further delineation into lost workdays, caregiver lost workdays and restricted activity days is not possible. Forgone future earnings due to premature death totaled \$132 million, with an average net present value of forgone income of \$355,000 for each fatality.

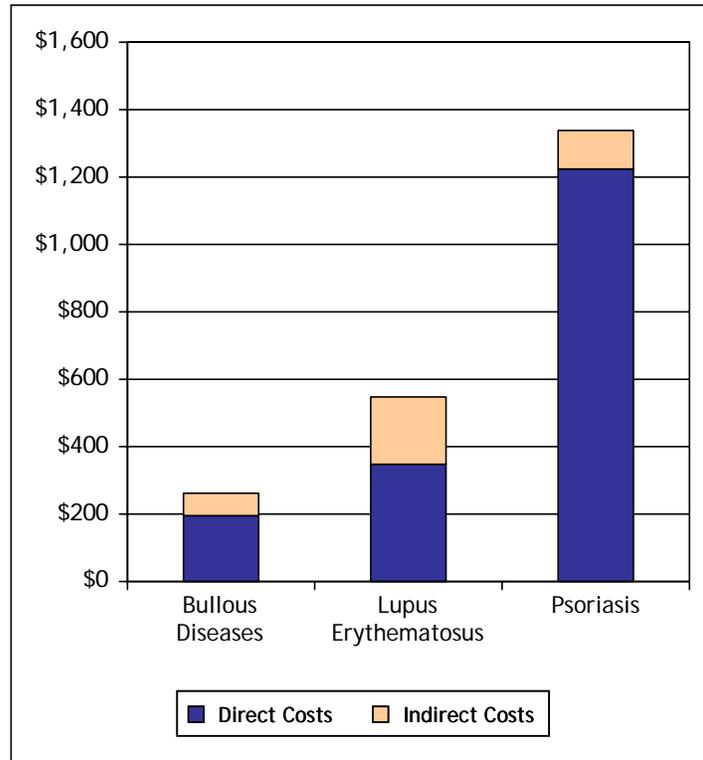
These estimates for productivity losses may be considerably lower than the actual losses due to lupus. These estimates only account for time lost in the pursuit of medical care, but it is estimated that 45% of patients with cutaneous lupus erythematosus experience some type of vocational handicap due to this condition. Moreover, cutaneous lupus erythematosus is reported to be the third most common cause of industrial disability due to dermatologic disease (after atopic dermatitis and contact dermatitis).²³⁰

Intangible Costs Due to Quality of Life Impact

This condition has further implications for quality of life. Individuals with lupus may also experience such co-morbid conditions as dementia and chronic fatigue. In a study of individuals with discoid lupus erythematosus, the mean score on the DLQI was 5.0. Willingness-to-pay is a quantitative way to measure the impact of a condition on a person's overall quality of life. In other words, the greater the willingness-to-pay, the more substantial the overall effect on quality of life. Based on a willingness-to-pay approach, individuals with lupus are willing to pay an average of \$1,014 annually for symptom relief. When applied to all individuals with lupus, the collective willingness-to-pay is \$36 million.

²³⁰ Patel 2002.

Figure 7.2. Annual Direct and Indirect Cost of Skin Conditions Due to Immune System Response, U.S. (\$ millions, 2004)



Immuno-bullous Diseases

Immuno-bullous skin diseases are characterized by blisters, referred to as bullae, which are formed as an immune system response to provocation by factors such as drugs, viruses, and other infectious agents. Family history may also play a role in susceptibility to this group of diseases. Common immuno-bullous diseases include the following.

- *Bullous pemphigoid* is a chronic condition with a genetic predisposition characterized by blister formation on any area of the skin, though most often in elbow and knee regions (and rarely in the mucous membranes).
- *Cicatricial pemphigoid* predominantly affects the mucous membranes, with cutaneous involvement of the head, neck, or sites of trauma, as well as potential oral lesions and chronic scarring conjunctivitis.
- *Dermatitis herpetiformis* is characterized by an associated gluten-sensitive disease of the intestinal tract and itchy, grouped blisters, most often in flexural areas.
- *Epidermis bullosa acqvista* is a rare, chronic subepidermal disease of skin and mucous membranes, characterized by redness and scarring, predominantly in areas of trauma.
- *Linear IgA dermatosis* is a subepidermal blistering disease that may be idiopathic (i.e., resulting from an unknown cause) or drug-induced, with a similar appearance to other blistering diseases.

- *Paraneoplastic pemphigus* is a rare condition with distinct histological and clinical presentation. It is histologically characterized by blisters occurring in the deeper part of the epidermis, above the basal layer, and immunopathologically characterized by specific autoantibodies.
- *Pemphigus vulgaris* is an intraepithelial blistering disease, with an immunogenetic predisposition, affecting the skin and mucous membranes and mediated by circulating autoantibodies directed against the epidermal cells that produce keratin.
- *Pemphigus foliaceus* is often a chronic condition characterized by superficial blisters formed after skin is rubbed, with little mucous membrane involvement.
- *Porphyria cutanea tarda* is the most common disorder of porphyrin metabolism, characterized by photosensitivity and vesiculo-bullous eruptions with scarring.

The blisters associated with bullous diseases can appear locally or cover the body more broadly. These blisters may vary in appearance from patches of mild redness to numerous pus-filled sores. In many cases, blistering is accompanied by severe pain, itching, burning, and stinging.^{231,232} Secondary symptoms may include fever, dehydration from fluid loss, and/or ulceration. Many patients may also experience minor to substantial scarring following bullous eruptions. Certain immuno-bullous diseases (e.g., linear IgA dermatosis, porphyria cutanea tarda, epidermolysis bullosa acquisita) are also associated with heightened risk of infection, debilitation, disfigurement, and even blindness, making timeliness of intervention and treatment essential to prevention of disability (which may be permanent) or premature death.

Accurate diagnosis and characterization of immuno-bullous diseases is important, as the clinical course and long-term prognosis for specific bullous diseases can vary considerably.²³³ Diagnostic assessment may include a thorough patient history and clinical assessment, as well as a variety of immune-related tests of skin (e.g., immunohistochemistry, immunofluorescence) and serum samples. Additional laboratory testing may be necessary to confirm the diagnosis or to identify other conditions that may involve blistering, such as lupus erythematosus.

Treatment for immuno-bullous diseases can be classified as rapid or slow acting, localized or systemic, and immunosuppressant (i.e., suppress the immune response)/immunomodulatory (i.e., capable of modifying or regulating one or more immune functions or anti-inflammatory). Examples of rapid methods of treatment include administration of steroids and plasmapheresis (i.e., plasma taken from donated blood with the remaining components, mostly red blood cells, returned to the donor), while slow acting treatments include management with dapsone (an antibiotic), azathioprine (an immunosuppressive agent), and tetracyclines (a group of antibiotics). Localized treatment generally involves topical care to address initial inflammation and follow-up measures, including prevention of trauma, soaking of the lesions, administration of corticosteroids

²³¹ Sami N, Yeh SW, Ahmed AR. Blistering diseases in the elderly: diagnosis and treatment. *Dermatol Clin* 2004;22(1):73-86.

²³² Bickle 2002.

²³³ Sami 2004.

and/or antibiotics. Conventional oral therapies used for treatment include anti-inflammatory agents, systemic corticosteroids, and immunosuppressive agents.²³⁴

Other treatment strategies for blistering diseases include, but are not limited to, avoidance of factors that exacerbate the condition (e.g., avoidance of sunlight for patients with porphyria cutanea tarda), dietary alterations (e.g., maintenance of a gluten-free diet for patients with dermatitis herpetiformis), plasmapheresis to decrease the level of causative auto-antibodies, and/or surgical excision of dead or contaminated tissue.^{235,236,237} Additionally, a variety of emerging therapies are currently being established for patients who develop side effects or fail to respond to conventional treatment modalities.²³⁸

Most immuno-bullous diseases have highly variable disease progression and presentation, as some patients with localized disease remain stable for several years without aggressive therapy, while others, despite treatment, can be chronically affected. Some diseases, such as bullous pemphigoid and dermatitis herpetiformis, can involve prolonged and multiple relapses following symptom management.²³⁹

Epidemiology

The epidemiology of most immuno-bullous diseases is relatively undocumented, as these diseases are not captured in any of the nationally representative datasets and smaller studies are infrequently reported. Depending on the particular immuno-bullous disease, prevalence may vary considerably among age, gender or ethnic groups. For example, women are affected with cicatricial pemphigoid twice as often as men, while pemphigus is thought to affect men and women equally.²⁴⁰

Incidence rates for this study were extracted from a review article of blistering diseases, including pemphigus, bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita, linear IgA bullous disease, dermatitis herpetiformis, and porphyria cutanea tarda.²⁴¹ Based on this review, the estimated overall incidence of immuno-bullous diseases is approximately 46 cases per 100,000 individuals per year. The majority of the incidence is attributable to one condition, dermatitis herpetiformis, which has an estimated incidence rate of 39 cases per 100,000 individuals per year.

Applying the overall incidence rate for immuno-bullous conditions to the 2004 U.S. population, yields an estimate of approximately 135,800 individuals diagnosed with an immuno-bullous condition during the calendar year. Again, incidence is reported here instead of prevalence due to paucity of information in the national databases and medical literature.

²³⁴ Ibid.

²³⁵ Bickle 2002.

²³⁶ Sami 2004.

²³⁷ Reynaert 2004.

²³⁸ Korman NJ. New and emerging therapies in the treatment of blistering diseases. *Dermatol Clin* 2000;18(1):127-37, ix-x.

²³⁹ Bickle 2002.

²⁴⁰ Sami 2004.

²⁴¹ Ibid.

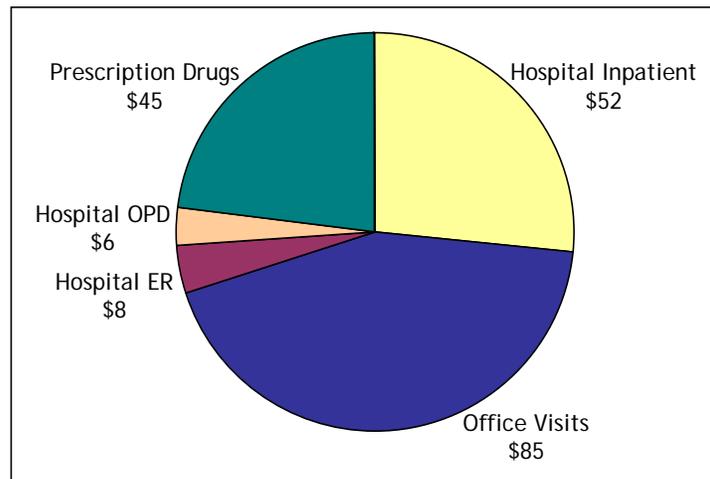
Mortality rates for immuno-bullous diseases vary considerably by disease. When analyzed collectively, the CDC's Compressed Mortality File attributed 165 deaths to immuno-bullous conditions in 2002. Mortality from these conditions is concentrated in the population aged ≥ 65 population, with 94% of deaths occurring in this age group.

Direct Costs

The total direct cost associated with treatment of immuno-bullous diseases is an estimated \$197 million (**Figure 7.3**). The primary site of care for these conditions was in physician offices, with 813,000 visits at a cost of \$85 million or around half of the total direct costs. The next most frequently accessed sites of service for immuno-bullous diseases are hospital outpatient departments and hospital emergency rooms. The number of admissions to the hospital outpatient department and hospital emergency rooms was 45,000 and 42,800, respectively (**Figure 7.5**). Care provided in hospital outpatient departments was responsible for \$6 million and care provided in emergency rooms was responsible for \$8 million of the total cost. Immuno-bullous diseases were listed as the primary diagnosis for 11,500 inpatient hospital stays, and identified as a non-primary diagnosis in 32,700 admissions, resulting in \$52 million in inpatient costs.

In addition to the costs of care for immuno-bullous diseases, the cost of prescription drugs was \$45 million, according to Scott-Levin data. Additionally, as noted above, immuno-bullous diseases is one of the disease categories for which certain significant drug costs, (i.e., for drugs sold through specialty pharmacies), are not captured by the datasets used in this study. Specific OTC costs for this category were not available from AC Nielson.

Figure 7.3. Annual Direct Cost of Immuno-bullous Diseases, U.S.
(\$ millions, 2004)



Indirect Costs

The indirect costs associated with immuno-bullous diseases due to lost productivity are estimated at \$65 million annually (**Figure 7.2**). Due to the lack of representative epidemiological data for these conditions, further delineation into lost workdays, restricted activity days, and lost caregiver workdays was not feasible. The total indirect costs include an estimated \$22 million in forgone future earnings due to premature death. Reflecting the

increase in mortality rate associated with advancing age, the average net present value of forgone income is only \$127,000.

Intangible Costs Due to Quality of Life Impact

As mentioned previously, blistering lesions can be extremely painful and can, in some cases, lead to life-threatening fluid loss, infection, and disfigurement. These diseases can also cause significant damage to the skin, including nail loss, pigmentary alteration, ocular lesions that may lead to blindness, and significant scarring that can substantially diminish quality of life and productivity. Few studies on these conditions with regard to quality of life exist, perhaps due to their low incidence rates. DLQI scores were found for individuals with bullous pemphigoid, who reported an average DLQI score of 6. For sake of comparison, this DLQI score indicates that individuals with bullous pemphigoid experience greater impairment to their quality of life than that due to vitiligo (DLQI=5.6), but less than that due to contact dermatitis (DLQI=7.5).

Psoriasis

Psoriasis is a common, chronic skin disorder characterized by patches of thick, raised patches of skin, called plaques. The term psoriasis comes from the Greek word “psora” which means “to itch,” and itching is the most commonly reported symptom of this disease.²⁴² Many of the complications of psoriasis can lead to difficulties in accomplishing normal daily tasks, such as climbing stairs, housework, gardening, and bathing, translating into substantial reductions in quality of life for patients with this disease.²⁴³

In addition to the effects on the skin, individuals with psoriasis may also experience abnormalities of finger or toe nails or burning of the eyes. Individuals with psoriasis are also at an increased risk of developing non-skin related disorders such as inflammatory bowel disease and non-Hodgkin lymphoma.²⁴⁴ Psoriasis may invade the joints, causing a type of inflammation, psoriatic arthritis, which is similar to rheumatoid arthritis.²⁴⁵

In psoriasis, the immune system mistakenly targets the body’s own cells, causing skin cells to replenish too rapidly. Overproduction of skin cells causes plaques to form since old skin cells are not able to slough off quickly enough. Though the exact cause of psoriasis is unknown, predisposition for the disease is thought to be genetically inherited, but can also be aggravated by environmental factors such as medications, sunburn, stress, and cold climate. The effects of stress on psoriasis flare-ups can be substantial. According to one systematic review, approximately 72% of patients experiencing a significant stressful event such as a death of a family member, hospitalization, or sexual assault in the month immediately prior to their first episode of psoriasis. The effect of stress appears to be

²⁴² Nickoloff BJ, Nestle FO. Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. *J Clin Invest* 2004;113(12):1664-75.

²⁴³ de Korte J, Sprangers MA, Mommers FM, Bos JD. Quality of life in patients with psoriasis: a systematic literature review. *J Invest Dermatol Symp Proc* 2004;9(2):140-7.

²⁴⁴ Naldi L. Epidemiology of psoriasis. *Curr Drug Targets Inflamm Allergy* 2004;3(2):121-8.

²⁴⁵ Nickoloff 2004.

magnified for children, with 90% reporting a major stressful event in the month before their first psoriasis episode.²⁴⁶

The severity of psoriasis can vary substantially from a few minor plaques that regress over time with little intervention to cases where plaques are not responsive to even the most aggressive therapies. An estimated 21% of psoriasis patients are classified as having moderate-to-severe disease.²⁴⁷ There is currently not a cure for psoriasis, so treatment focuses on symptom management. For mild cases of psoriasis, numerous OTC products can be used at home, including dandruff shampoos, cortisone creams, antifungal lotions, and lotions containing coal tar. More serious cases of psoriasis are usually managed with topical corticosteroids, topical retinoids, phototherapy, and PUVA photochemotherapy. The most severe psoriasis cases are treated with immunosuppressive medications such as methotrexate and cyclosporine or biologic therapy.²⁴⁸ In rare circumstances, psoriasis can be life-threatening when lesions cover most of the body. In these cases, hospitalization is usually necessary to prevent complications such as infection, septic shock, or death.²⁴⁹

Epidemiology

The 1996 NHIS included a question concerning psoriasis over the preceding 12 months. The prevalence of this condition was reported to be 1,100 cases per 100,000 persons. This estimate falls within other reported prevalence rates, which range from 800 to 1,400 cases per 100,000.²⁵⁰ More recent reports indicate that the prevalence may be higher. A telephone-based survey of 27,220 individuals concluded that 2.2% of the population age 18 and older has been diagnosed by a physician as having psoriasis.²⁵¹ Reports in the literature indicate that psoriasis is slightly more common in men than women, and that ethnic variations have not been found. Due to environmental factors, psoriasis is suspected to more commonly affect individuals living in urban areas.²⁵² Applying age- and sex-adjusted rates derived from the NHIS data to the 2004 U.S. population yields an estimate of 3.14 million people of all ages with psoriasis. Applying the results of the telephone survey would suggest that as many as 4.55 million people age 18 and older are affected by the condition.

Psoriasis is rarely associated with mortality, with only 36 deaths reported due to this condition in the 2002 Compressed Mortality File.

²⁴⁶ Gupta MA, Gupta AK. Psychiatric and psychological co-morbidity in patients with dermatologic disorders: epidemiology and management. *Am J Clin Dermatol* 2003;4(12):833-42.

²⁴⁷ Crown WH. The cost of psoriasis. *Managed Care* 2003;12(5):10-13.

²⁴⁸ Lehrer M. Medline plus medical encyclopedia: psoriasis. Bethesda, MD: U.S. National Library of Medicine and National Institutes of Health, 2002. Accessed September 2004. <http://www.nlm.nih.gov/medlineplus/ency/article/000434.htm>.

²⁴⁹ Ibid.

²⁵⁰ Naldi 2004.

²⁵¹ Stern RS, Nijsten T, et al. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. *J Invest Dermatol Symp Proc* 2004;9:136-139.

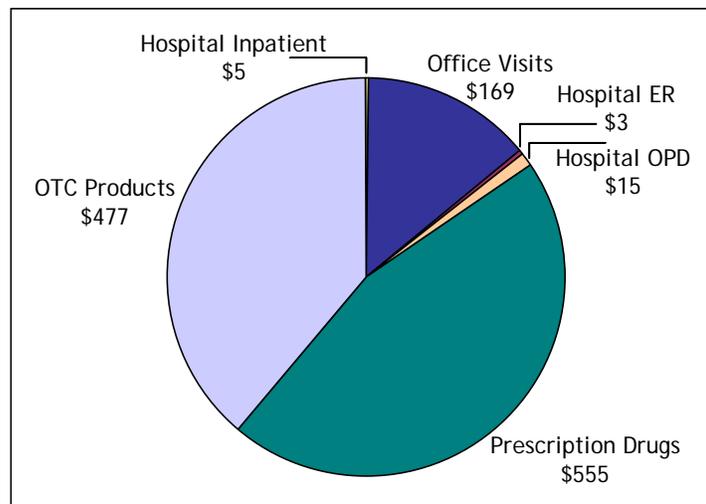
²⁵² Ibid.

Direct Costs

The total direct cost of treatment associated with psoriasis is an estimated \$1.2 billion (**Figure 7.4**). OTC treatment options for psoriasis cost \$477 million and account for 39% of the expenditures attributed to this disease. Prescription drug costs also account for a sizeable portion of expenditures for this condition with \$555 million spent on over 2.7 million prescriptions. As noted above, psoriasis is one of the diseases for which certain significant drug costs, (i.e., for drugs sold through specialty pharmacies), are not captured by the datasets used in this study.

The primary source of care for psoriasis is the physician's office, with nearly 2.3 million visits (**Figure 7.5**). The cost attributed to these visits for physician's time and services was \$169 million. Outpatient hospital stays are the next most frequently accessed means of care, responsible for \$15 million of the total direct cost. Inpatient hospital stays with psoriasis as the primary diagnosis were relatively infrequent, with 1,700 admissions. In comparison, there were 36,400 inpatient hospital stays with psoriasis as a non-primary diagnosis. In total, care provided through the inpatient hospital setting cost \$5 million.

Figure 7.4. Annual Direct Cost of Psoriasis, U.S.
(\$ millions, 2004)



Indirect Costs

Total indirect costs for psoriasis due to lost productivity are estimated at approximately \$114 million annually, including \$9.6 million in forgone future earnings due to premature death (Figure 7.2). This condition is responsible for \$51 million in lost workdays, \$32 million in restricted activity days for those who actually have psoriasis, and \$22 million in caregiver lost workdays. This estimate of lost productivity may be low since it is heavily reliant on time lost in pursuit of medical care, and does not consider productivity lost for other condition-related factors. The productivity lost due to the physical effects of psoriasis may be considerable, as a 2002 survey conducted by the National Psoriasis Foundation

indicates that 26% of individuals with moderate to severe psoriasis have been forced to change or discontinue their normal daily activities due to their condition.²⁵³

Intangible Costs Due to Quality of Life Impact

Psoriasis has a substantial impact on individual quality of life including increased incidence of anxiety, depression, poor self-image, and lack of self-confidence. On the DLQI, individuals with psoriasis had an average score of 8.8. Individuals with psoriasis report more impairment from their condition than individuals with cutaneous fungal infections (DLQI=5.5), but less than individuals with atopic dermatitis (DLQI=12.2).

Willingness-to-pay is a quantitative way to measure the impact of a condition on a person's overall quality of life. In other words, the greater the willingness-to-pay, the more substantial the overall effect on quality of life. Based on a willingness-to-pay perspective, individuals with psoriasis are willing to pay \$1,114 per year for symptom relief. When adjusted for disease severity and applied to the entire population of psoriasis sufferers, the aggregate willingness-to-pay for symptom relief is \$2.3 billion per year.

Figure 7.5. Health Care Utilization for Skin Conditions Due to Immune System Response

| Disease | Inpatient Hospital Stays | Inpatient Hospital Stays (primary diagnosis only) | Outpatient Hospital Visits | Emergency Room Visits | Physician Office Visits |
|-------------------------|--------------------------|---------------------------------------------------|----------------------------|-----------------------|-------------------------|
| Lupus erythematosus | 136,300 | 19,000 | 184,200 | 47,800 | 1,100,100 |
| Immuno-bullous diseases | 32,700 | 11,500 | 45,000 | 48,900 | 813,000 |
| Psoriasis | 36,400 | 1,700 | 158,000 | 18,800 | 2,263,900 |

Source: 2002-2003 NAMCS, NHAMCS, NHIS, NHDS adjusted to the 2004 US population

²⁵³ Benchmark survey on psoriasis and psoriatic arthritis. Washington, DC: National Psoriasis Foundation, 2002. Accessed January 26, 2005. <http://www.psoriasis.org/files/pdfs/press/npfsurvey.pdf>

Chapter 8: Exogenous Skin Conditions

This chapter presents the clinical, epidemiological, and economic estimates of the burden of skin conditions caused by injury or adverse drug reactions, collectively referred to here as exogenous skin conditions. This chapter addresses skin ulcers and wounds, solar radiation (resulting in sunburns), and cutaneous drug eruptions.

Skin Ulcers and Wounds

Wounds are typically classified as either acute, which heal within three months, or chronic, which take longer than three months to heal and can last a lifetime.²⁵⁴ Skin ulcers, including venous ulcers, arterial ulcers, neuropathic ulcers, and pressure ulcers, are the most common chronic skin wounds and pose significant infection risks to patients.²⁵⁵ Other significant skin wounds include traumatic wounds such as frostbite and thermal burns.

Skin ulcers occur frequently in certain health care settings (e.g., hospitals, nursing homes). The most common skin ulcers include the following.

- **Arterial ulcers** result when complete or partial arterial blockage leads to insufficient oxygenation of the skin causing tissue necrosis and/or ulceration. Symptoms can include substantial pain, pulselessness of the extremity, skin atrophy, and delayed capillary return time.
- **Neuropathic ulcers** are most commonly seen in diabetic patients, occurring when damage to nerve fibers leads to ulceration. These ulcers typically appear on the bottom of patients' feet.
- **Pressure ulcers** develop when continuous pressure on a bony site, such as the bony protrusion above the buttocks, obstructs healthy blood flow, leading to tissue necrosis.²⁵⁶ These lesions can emit a foul odor and progress to a state of necrosis to the bone. These skin ulcers arise typically in nursing homes and critical care units. They can develop in 2 to 6 hours, so identification of and preventive care for at-risk individuals is crucial.²⁵⁷
- **Venous ulcers** are open sores of the lower leg and foot caused by sustained venous hypertension, resulting in inflammation, tissue fibrosis, and, ultimately, ulceration.²⁵⁸

Thermal burns are caused by any external heat source capable of raising the temperature of the skin, and burns may involve other tissues, such as fat, muscle, or bone depending on severity. Common causative sources include flames and hot liquids, objects, or gases that come in contact with the skin. Burns are classified by their depth and extent of tissue damage. First-degree burns affect only the top layer of skin, while second-degree burns affect the dermis (middle layer of skin), and third-degree burns involve all layers of skin

²⁵⁴ Bello 2000.

²⁵⁵ Ibid.

²⁵⁶ Lyder CH. Pressure ulcer prevention and management. JAMA 2003;289(2):223-6.

²⁵⁷ Ibid.

²⁵⁸ Simon DA, Dix FP, and McCollum CN. Management of venous leg ulcers. BMJ 2004;328:1358-62.

and potentially nerve endings or other tissue. Severe thermal or other burns that cover large portions of the body can be particularly complicated and costly to treat, often requiring specialized care in regional burn centers.

Frostbite is a fairly common, though severe, form of cold injury in which localized freezing of tissues occurs.²⁵⁹ While the feet are most likely to be damaged by frostbite, the ears, nose, cheeks, and penis may also be affected. Initial clinical manifestations are similar and generally include pain or discomfort, mild itching, loss of range of motion, and edema, with eventual numbness of the tissue. Tissue appears white or blue-white and firm to the touch. Often, the severity of damage cannot be determined for several days. Additionally, rapid re-warming of the tissue with dry heat can lead to additional tissue injury, such as severe pain, burning, and even gangrene and tissue necrosis.²⁶⁰

Diagnosis of skin wounds can often be made through examination of visible symptoms (e.g., location and appearance of sores, degree of tissue death, level of blistering), along with analysis of medical history and coexisting medical conditions. Further examination and assessment of blood flow can be made through imaging studies, such as angiography, radiography, or Doppler duplex scanning.²⁶¹ Additionally, some tests may be performed to assess the boundary of tissue viability.

The primary goals of skin wound healing include rapid closure and establishment of a functional scar; treatments for this vary depending on the diagnosis and severity of the condition. Wound management typically begins with debridement of any dead tissue below the skin, followed by immediate wound coverage with synthetic and natural dressings, as well as remediation of the underlying problems (e.g., hyperglycemia, restoration of adequate tissue perfusion, control of infection).²⁶²

A great variety of moisture-retentive dressings, which can reduce infection rates and pain, are available for acute and chronic wounds. For example, there are more than 300 types of dressings currently marketed for pressure-ulcer care alone.²⁶³ Reconstructive surgery may be necessary in some cases, and a variety of potential skin substitutes can be used to promote healing of more extensive, life-threatening wounds and burns. Systemic and topical antibiotics are generally used to prevent/treat systemic infection. Pharmacologic agents are used as adjunctive therapies for chronic wounds.

Treatment of frostbite differs somewhat from treatment of other skin wounds, such as ulcers and burns. Initially, removal of the patient from the hostile environment is necessary. Subsequently, analgesics can be administered for pain, and the affected tissue is generally immersed in a warm water bath for slow, continuous re-warming. Upon completion of the re-warming process, circulation must be re-established, the affected area is elevated, and steps are taken to avoid infection and abrasion, including various topical creams/ointments (e.g., anti-adrenergic, steroidal) and oral medicines are involved in treatment. Patients with second- and third-degree frostbite are typically hospitalized and treated with daily whirlpool baths, pain relieving medications, and physical therapy. In severe cases, most

²⁵⁹ Heimbach D, Gibran N. Miscellaneous burns and cold injuries. ACS Surgery 2004 © 2003 WebMD Inc.

²⁶⁰ Reamy BV. Frostbite: review and concepts. J Am Board Fam Pract 1998;11(1):34-40.

²⁶¹ Simon 2004.

²⁶² Singer 1999.

²⁶³ Lyder 2003.

often for cases of persistent infection and sepsis, amputation or surgical debridement and skin grafting may be necessary.²⁶⁴

Epidemiology

Prevalence of pressure ulcers was obtained from a study of the 1999 National Pressure Ulcer Prevalence Survey, which assessed 42,817 patients in acute care hospital settings for pressure ulcers of nine different anatomical sites, including the sacrum and heel. The reported crude prevalence rate in this study was 1,480 cases per 100,000 individuals. Females were more likely to be affected than males, accounting for 54% of pressure ulcer patients. Patients over the age of 60 were at highest risk for developing a pressure ulcer, with 78% of ulcers occurring in this age category.²⁶⁵ The prevalence rates estimated in this study may underreport the actual occurrence of this condition, since this study only surveyed acute care facilities. Individuals receiving care in skilled nursing facilities, other long-term care facilities, and at home are also known to be at an increased risk of developing pressure ulcers.

Applying the age-specific prevalence rates from the 1999 National Pressure Ulcer Prevalence Study to the 2004 U.S. population yields an estimate of 3.2 million individuals having experienced at least one pressure ulcer during the year. Pressure ulcers were listed as the underlying cause of death in 1926 cases in the Compressed Mortality File for 2002. From the data in the CMF, it was estimated that the crude mortality rate of pressure ulcers is 0.665 deaths per 100,000 individuals. Mortality increased substantially with increasing age, with 92% of fatalities occurring in the over 65 population.

Prevalence statistics for burns were calculated based on data from the National Electronic Injury Surveillance System-All Injury Program (NEISS-AIP) of the CDC National Center for Injury Prevention. The NEISS-AIP reported a crude prevalence rate of 2,517 burn cases per 100,000 people for 2003. Children under the age of four were at highest risk for experiencing a burn, with a prevalence rate of 360 cases per 100,000 individuals for this age group. Males were also at higher risk for experiencing a burn, with 54% of cases attributable to this group.²⁶⁶ Applying this prevalence rate to the 2004 U.S. population yields an estimate of 1.6 million individuals having experienced at least one thermal burn during the calendar year.

Mortality from burns was estimated based on the NEISS-AIP mortality file, as opposed to the Compressed Mortality File, which has low cell counts for this condition. A total of 3,600 deaths were recorded in the NEISS-AIP in 2002 for a crude mortality rate of 1.3 deaths per 100,000 individuals. Males were 1.6 times more likely to die from a burn injury than females.²⁶⁷

²⁶⁴ Ibid.

²⁶⁵ Amlung SR, Miller WL, Bosley LM. The 1999 National Pressure Ulcer Prevalence Survey: a benchmarking approach. *Adv Skin Wound Care*. 2001 Nov-Dec;14(6):297-301.

²⁶⁶ Web-based Injury Statistics Query and Reporting System (WISQARS). Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control Accessed January 31, 2005. www.cdc.gov/ncipc/wisqars.

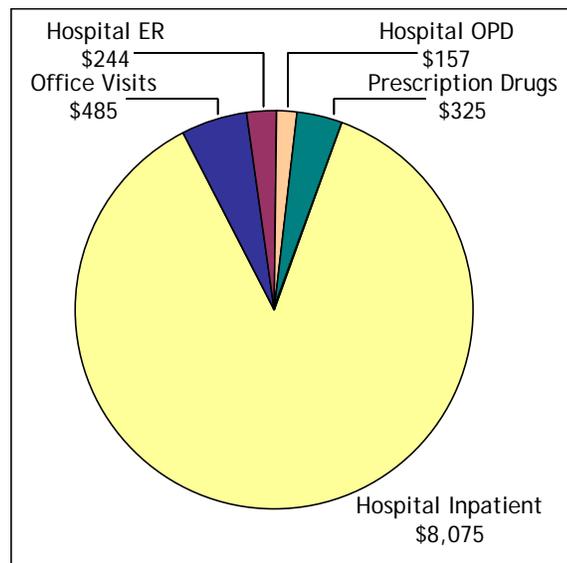
²⁶⁷ Web-based Injury Statistics Query and Reporting System (WISQARS) 2005.

Direct Costs

The total direct cost of skin ulcers and wound healing is estimated at \$9.7 billion dollars, making this category of skin conditions the most expensive of all those under review in this study (**Figure 8.1**). The vast majority of costs associated with these conditions are due to inpatient hospital stays, representing 83% of total costs at \$8 billion. There were 329,400 hospital stays in which a skin ulcer or wound was listed as the primary diagnosis (**Figure 8.5**). When non-primary diagnoses of these conditions are included, the total number of hospital stays exceeds 1 million admissions.

Skin ulcers and wounds are also frequently seen in emergency rooms, where nearly 1.7 million visits were made for these conditions in 2004. The total cost of care provided in non-inpatient settings was more than \$886 million. Prescription drug costs represented only 3% of total costs for skin ulcers and wound healing, but procedure costs for this category were significant at \$7.6 billion, or 78% of total direct costs.

Figure 8.1. Annual Direct Cost of Skin Ulcers and Wounds, U.S.
(\$ millions, 2004)



Indirect Costs

The indirect costs associated with skin ulcers and wounds are substantial, with an estimated \$2.5 billion in lost productivity alone (**Figure 8.2**). This includes \$172 million in lost workdays and \$152 million in restricted activity days for individuals who actually have the conditions. An additional \$102 million is attributable to caregiver lost workdays.

Forgone future earnings due to premature death attributable to skin ulcers and wounds have a great net present value of \$2.1 billion. Mortality due to skin ulcers tends to occur over the age of 65, meaning that the average net present value of foregone future earnings is only \$150,000 compared to the net present value of \$483,000 for burn fatalities which tend to occur more uniformly across age categories.

Intangible Costs Due to Quality of Life Impact

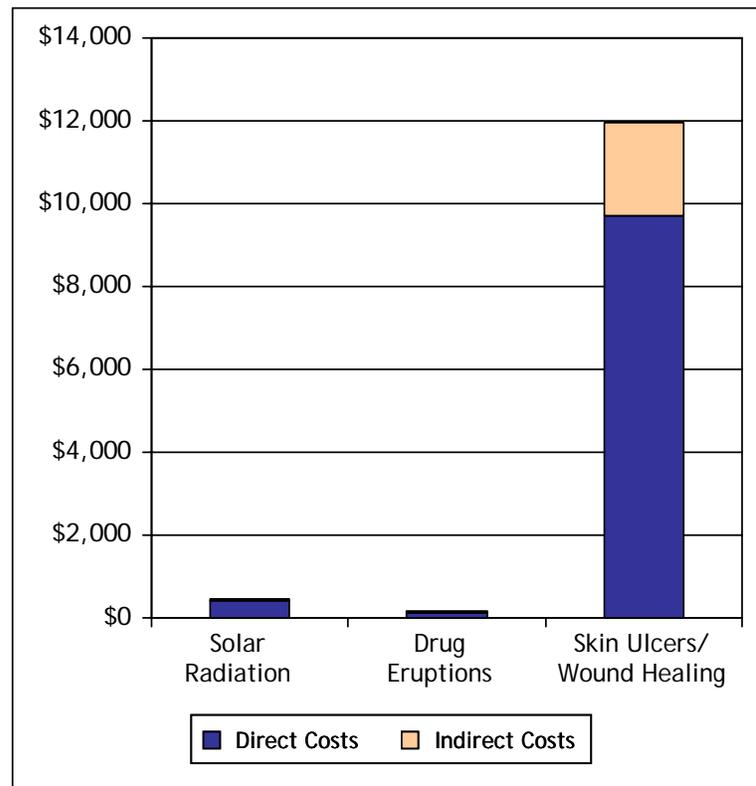
Skin ulcer and wound care has a substantial impact on quality of life due to pain, prolonged hospitalization, daily dressing changes, and decreased mobility. Individuals with skin ulcers score an average of 6.9 on the DLQI. Individuals with skin ulcers experience greater diminishment to quality of life than individuals with actinic keratosis (DLQI=3.6), but less than individuals with psoriasis (DLQI=8.8). The score may underestimate the quality of life effects for all individuals with pressure ulcers since it was derived from a survey of patients in a primary care setting,²⁶⁸ who were less likely to be experiencing severe pressure ulcers.

Willingness-to-pay is a quantitative way to measure the impact of a condition on a person's overall quality of life. In other words, the greater the willingness-to-pay, the more substantial the overall effect on quality of life. When the effects on quality of life are adjusted for duration and severity of illness and viewed from a willingness-to-pay perspective, individuals with skin ulcers would be willing to pay an aggregate of \$968 million annually for relief of their symptoms.

DLQI scores for other types of exogenous skin conditions, (e.g. frostbite and thermal burns) were not available in the literature and corresponding utility values were also lacking. Certainly, thermal burns, especially those that are disfiguring to the face and other visible body parts, can have a substantial psychosocial effect. Furthermore, depending on location and severity, burns and frostbite can be debilitating, affecting vocational and leisure activities. While accounting for these effects in the overall economic burden of skin ulcers and wounds was not feasible given the limitations in quality of life data for these conditions, their often severe effects on patients are significant.

²⁶⁸ Harlow D, Poyner T, Finlay AY, Dykes PJ. Impaired quality of life of adults with skin disease in primary care. *Br J Dermatol* 2000 Nov;143(5):979-82.

Figure 8.2. Annual Direct and Indirect Cost of Exogenous Skin Conditions, U.S. (\$ millions, 2004)



Skin Damage Resulting from Sun Exposure

Exposure to the sun's radiation can cause skin problems ranging from various degrees of sunburns to the photosensitivity disorders.²⁶⁹ Other skin conditions arising from long-term sun exposure, such as actinic keratosis, nonmelanoma skin cancer, and melanoma, are discussed in Chapter 4 of this report (and not included in this section). Sunburn is a common and acute reaction of the skin to UV radiation exposure, and ranges from reddening of the skin to swelling, blistering and pain or itching.²⁷⁰ The visible effects of acute solar radiation are observable after 3-5 hours of exposure and become more intense approximately 1 day after exposure before beginning to fade on day three.²⁷¹

Polymorphous light eruption (PMLE) is the most common type of photodermatosis, and is characterized by recurrent and sometimes delayed reactions to the sun.²⁷² Following a little as 30 minutes of sun exposure, the skin of an individual with PMLE may appear red, with papules and plaques. Chronic actinic dermatitis is a chronic photosensitivity disorder which is probably immunologically mediated.²⁷³ Tests are used to determine the exacerbating wavelengths as well as any photo-contact allergens by phototesting (diagnostic

²⁶⁹ Dawe RS, Ferguson J. Diagnosis and treatment of chronic actinic dermatitis. *Dermatol Ther* 2003;16(1):45-51.

²⁷⁰ Han A, Maibach HI. Management of acute sunburn. *Am J Clin Dermatol* 2004;5(1):39-47.

²⁷¹ *Ibid.*

²⁷² Tutrone WD, Spann CT, Scheinfeld N, Deleo VA. Polymorphic light eruption. *Dermatol Ther* 2003;16(1):28-39.

²⁷³ Dawe 2003.

exposure to specific forms of light) and photo-patch testing (trial applications of potential allergens to the skin followed by exposure to UV).

With varying levels of effectiveness, means used to protect against solar radiation include physical protection (i.e., hats, long sleeves and pants that cover the skin), and sunscreens.²⁷⁴ However, reflecting cultural factors in part, 47% of the U.S. Caucasian population is unlikely to use any form of protection against sun exposure.²⁷⁵ Additional attention to the avoidance of allergens is also important in the prevention of chronic actinic dermatitis.²⁷⁶

When exposure to the sun does occur, sunburn and chronic actinic dermatitis can be treated with topical ointments (i.e. corticosteroids) and antihistamines. Many treatments can reduce the redness caused by solar radiation, including topical and systemic steroids, aspirin and ibuprofen, and emollients such as petroleum jelly and water-based ointments.²⁷⁷ Antibiotics may be used as well when a sunburn lesion becomes infected. In severe cases of chronic actinic dermatitis, systemic immunosuppressive drugs may also be applied.

Epidemiology

Prevalence rates for sunburn were obtained from three methodologically sound studies reported in the literature. The first used the 2000 NHIS to determine the rate of sunburn among adults. The second study involved a telephone survey to determine the rate of sunburn among adolescents ages 11 to 18. Another study estimated the rate of sunburn of the infant to age 11 cohort with a national telephone survey.²⁷⁸

From the Hall 2003 retrospective study of the 2000 NHIS, it is estimated that 36% of adults experience at least one sunburn annually.²⁷⁹ This study indicated that Caucasians, males, and younger adults are at the highest risk of developing sunburns. The prevalence among adolescents is estimated to be considerably higher than among adults. From the national survey of 1,192 youths ages 11 to 18 (and their parents), level of sun exposure, sunburn prevention methods, and attitudes concerning sun exposure, it was found that 72% of youths surveyed experienced at least one sunburn annually. Of these youths, 30% experienced at least three sunburns, and 12% experienced at five or more sunburns.²⁸⁰ This survey found that those at a higher risk of sunburn included those with outdoor jobs, those who viewed a tan as appealing, and those who perceived minimal benefit from protective measures such as sun screen. A separate national survey of 1,052 parents reported that 43% of children under the age of 11 experienced one or more sunburns over the past year.²⁸¹ Applying these rates to the 2004 U.S. population yields an estimate of 123 million individuals who experienced at least one sunburn during the calendar year.

²⁷⁴ Han 2004.

²⁷⁵ Ibid.

²⁷⁶ Dawe 2003.

²⁷⁷ Han 2004.

²⁷⁸ Hall HI, Jorgensen CM, McDavid K, Kraft JM, Breslow R. Protection from sun exposure in US white children ages 6 months to 11 years. *Public Health Rep.* 2001 Jul-Aug;116(4):353-61.

²⁷⁹ Hall HI, Saraiya M, Thompson T, et al. Correlates of sunburn experiences among U.S. adults: results of the 2000 national health interview survey. *Public Health Rep* 2003;118(6):540-9.

²⁸⁰ Davis KJ, Cokkinides VE, Weinstock MA, et al. Summer sunburn and sun exposure among US youths ages 11 to 18: national prevalence and associated factors. *Pediatrics* 2002;110(1 Pt 1):27-35.

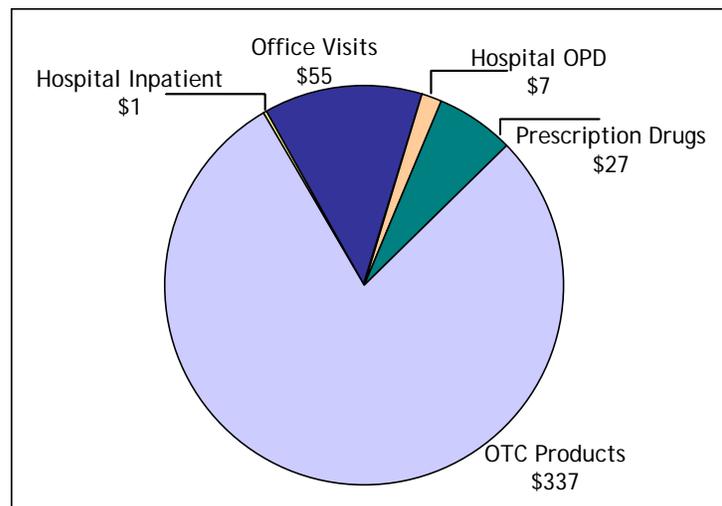
²⁸¹ Hall HI, Jorgensen CM 2001.

Sunburn is not a condition significantly associated with mortality; as no deaths were attributed to this cause in the CDC's Compressed Mortality File in 2002.

Direct Costs

The total direct cost associated treatment for solar radiation is \$434 million (**Figure 8.3**). Of these total costs, 78%, or \$337 million, was attributable to OTC costs. Care for solar radiation is generally not provided in physician offices, emergency rooms, or outpatient hospital departments (**Figure 8.5**). This limited utilization, coupled with the high proportional cost associated with OTC products, suggests that solar radiation damage to the skin is frequently self-treated by affected individuals. Solar radiation was listed as a diagnosis in 649,400 physician office visits and 26,200 hospital outpatient visits for a cost of \$62 million. Solar radiation was listed as a diagnosis in 1,400 hospital admissions, with only 200 listing this as the primary diagnosis. The inpatient hospital cost associated with solar radiation is less than \$1 million.

Figure 8.3. Annual Direct Cost of Damage Due to Sun Exposure, U.S. (\$ millions, 2004)



Indirect Costs

Indirect costs associated with lost productivity due to the pursuit of medical care for sunburn are estimated at \$33 million annually (**Figure 8.2**). Since many sunburns are treated with OTC products without intervention from a physician, and are therefore not captured by conventional data sources, the actual lost productivity costs associated with this condition may be significantly higher.

Intangible Costs Due to Quality of Life Impact

There is currently no quantitative information concerning the effects of sunburn on quality of life, most likely due to its acute nature and the perception that sunburns are more of an inconvenience than a significant medical condition. Therefore, a conservative estimate based on comparison of this condition to conditions with similar outward manifestations and effects on daily activities was made, resulting in an annual willingness-to-pay for symptom relief of \$993 million annually.

Therefore, it was not feasible to estimate the willingness-to-pay for symptom relief for those with sunburns.

Cutaneous Drug Eruptions

Cutaneous drug eruptions (CDE) are adverse drug reactions that manifest on the skin. CDE can be caused by various prescription and OTC drugs (e.g., topical corticosteroids, certain analgesics). Reactions include any detrimental change in the function or structure of the skin, its appendages, or mucous membranes.²⁸² Cutaneous drug eruptions are the most frequently occurring adverse drug reactions, as approximately 30% of all adverse drug reactions manifest in the skin, although many skin reactions can occur along with multi-organ involvement.²⁸³ Diagnosing a CDE can be challenging, as these reactions often look like other skin diseases (e.g., bacterial infections, psoriasis, autoimmune blistering diseases) and may be the result of a single drug or combination of drugs.^{284,285}

Many cutaneous ADRs have an allergic or toxic basis, though the cause of many reactions is unknown.²⁸⁶ Potential causes of these reactions include pharmacologic side effects, overdose, drug accumulation (i.e., drug buildup in the body over time), drug-drug interactions, microbiologic imbalance, hypersensitivity to certain medications, exacerbations of existing disease, and autoimmune-like reactions.²⁸⁷ Reaction rates tend to be highest for antibiotics. Effects can range from small papules (small, solid, usually inflamed elevations of the skin that do not contain pus) to large, pus-filled blisters or dead tissue. Additionally, these skin manifestations can be accompanied by severe fever, burning sensations, and discomfort.²⁸⁸ Specifically, the documented incidence of cutaneous drug reactions reported as “potentially severe” is around 2%, though this rate varies across health care settings.^{289,290} While most reactions are mild, the most severe cutaneous drug reactions can be life threatening.

²⁸² Drake 1996.

²⁸³ Nigen S, Knowles SR, Shear NH. Drug eruptions: approaching the diagnosis of drug-induced skin diseases. *J Drugs Dermatol* 2003;2(3):278-99.

²⁸⁴ Svensson CK, Cowen EW, Gaspari AA. Cutaneous drug reactions. *Pharmacol Rev* 2001;53(3):357-79.

²⁸⁵ Nigen 2003.

²⁸⁶ Lee A, Thomson J. Adverse drug reactions. *The Pharmaceutical Journal* 1999;262(1):357-62.

²⁸⁷ Drake 1996.

²⁸⁸ Bigby M. Incidence, prevalence, and the rates of cutaneous reactions to drugs. *J Eur Acad Dermatol Venereol* 2000;14(6):435.

²⁸⁹ The World Health Organization (WHO) defines serious adverse drug reaction as a drug-related that “results in death, requires hospitalization or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening.”

²⁹⁰ Bachot N, Roujeau JC. Differential diagnosis of severe cutaneous drug eruptions. *Am J Clin Dermatol* 2003;4(8):561-72.

Drug eruptions can manifest in a variety of ways (e.g., blisters, hives, rashes) and can be classified as follows.²⁹¹

- **Acute generalized exanthematous pustulosis** is a rash characterized by small pustules and fever; examples of common causative drugs: quinolones, itraconazole, penicillin and its derivatives.
- **Drug hypersensitivity syndrome** is a complex and potentially life-threatening condition characterized by delayed onset of exanthema, with fever and internal organ involvement. Examples of common causative drugs are aromatic anticonvulsants, sulfadiazine, and minocycline.
- **Drug-induced acne** is also referred to as acneiform drug eruption because eruptions mimic acne vulgaris, most often beginning in skin creases or the face, and are frequently accompanied by fever and leucocytosis (i.e., increase in white blood cell count).
- **Drug-related bullous eruptions** are blistering reactions associated with the administration of a drug, including drug-induced autoimmune disorders, Stevens-Johnson Syndrome (SJS), erythema multiforme, and toxic epidermal necrolysis (TEN), all of which are also classified as bullous disorders. Examples of common causative drugs are captopril, furosemide, and sulfasalazine.
- **Exanthematous drug eruptions** typically accompany treatment for infectious disease. They are often characterized by a measles-like rash on the upper trunk or head, spreading down the limbs, and often accompanied by itching. Examples of common causative drugs are allopurinol, barbiturates, and naproxen.
- **Fixed drug eruptions** are a common, distinctive disease characterized by sharply defined, scaly patches (sometimes with central blisters) that may be accompanied by burning or stinging. Examples of common causative drugs are acetaminophen, dapsone, and tetracyclines.
- **Lichenoid drug eruptions** mimic lichen planus, a skin condition characterized by the eruption of flat-topped, shiny, violet colored papules, sometimes with oral involvement. Examples of common causative drugs are beta blockers, gold, and thiazides.
- **Photosensitivity drug eruptions** are caused by the combined effect of sunlight and a chemical, often characterized by hyperpigmentation and blistering; comprising phototoxicity and photoallergy reactions. Examples of common causative drugs are amiodarone, ketoprofen, and promethazine.
- **Serum sickness-like reactions** are a type III immune complex disease, characterized by hives-like or measles-like eruptions, purpura (i.e., hemorrhages in the skin and mucous membranes that result in of purplish spots/patches) and/or ulceration, along with a number of potential side effects (e.g., fever, gastrointestinal problems, malaise). Examples of common causative drugs are ampicillin, bupropion, and cefaclor.
- **Urticaria** is a transient, benign skin eruption, also known as angioedema, characterized by a few-to-multiple widespread papules, most often on the lips, eyes, and mucous membrane. Examples of common causative drugs are ACE inhibitors,azole antifungals, and NSAIDs.

²⁹¹ Nigen 2003.

Exanthematous drug reactions are the most common cutaneous drug eruptions, comprising about 95% of all cases. These drug reactions typically begin within a few weeks of medication introduction and resolve gradually within 1-2 weeks after medication use has ceased.²⁹²

Because different mechanisms of action underlie CDEs, the severity of reactions varies considerably by drug and individual response. Thus, a thorough patient history and analysis of all drugs taken intermittently or on an as needed basis (e.g., pain medications, sedatives, OTC medications) must be considered. Initial clinical impressions are generally based upon morphology (e.g., blistering, pustular, or hive-like sores) and the presence of potentially contributory co-morbid conditions.²⁹³ Because most skin reactions occur soon after the introduction of the causative drug, the timing of reactions is often an important diagnostic tool. Non-cutaneous warning signs (e.g., hypotension, malaise, fever, rapid heart beat) are considered with morphologic presentation. In many cases, clinical laboratory tests are then performed to confirm the suspected causative agent, such as skin and blood cultures and chemical or molecular assays.

Treatment of CDEs generally consists of discontinuation or dose alteration of the offending drug, along with provision of the necessary supportive care to reduce symptoms and prevent additional reactions. ADRs can lead to significant problems in organs other than the skin, so identification of skin problems often informs clinicians of potential systemic problems and effects that require further treatment. Topical and/or systemic corticosteroids, antihistamines, emollients, and topical anti-itching agents, among other medications, are frequently used to treat the symptomatic effects of drug eruptions. Surgical care is occasionally needed in severe cases; for example, surgical excision of dead tissue may be necessary in cutaneous necrosis to prevent downstream infection and health complications.²⁹⁴ To reduce likelihood of ADRs, and many health systems have instituted technologies such as bar coding systems and computerized physician order and prescription entry systems.²⁹⁵

Epidemiology

Because CDEs can be attributed to a variety of drug or drug interaction scenarios and because many drug eruptions may go unreported, data documenting the incidence, cost, and health effects of these conditions are sparse.²⁹⁶ Health care providers have revealed misconceptions about reporting ADRs for numerous reasons, including the difficulty in determining the drug responsible for the ADR, perception that all serious ADRs are reported by the time a drug hits the market, and the assumption that these reactions should only be reported if the provider is absolutely certain of the drug related to the ADR.²⁹⁷ Despite data limitations, ADRs are estimated to prompt 3-8% of all hospital admissions and

²⁹² Ibid.

²⁹³ Ibid.

²⁹⁴ Drake 1996.

²⁹⁵ Preventable adverse drug reactions: a focus on drug interactions. Rockville, MD: Center for Drug Evaluation and Research, FDA, 2002. Accessed November 1, 2004.

²⁹⁶ Drake 1996.

²⁹⁷ Preventable adverse drug reactions: a focus on drug interactions. Rockville, MD: Center for Drug Evaluation and Research, FDA, 2002. Accessed November 1, 2004.

<http://www.fda.gov/cder/drug/drugReactions/default.htm>.

occur in as many as 5% of hospitalized patients (of which 1 in every 1000 may have a cutaneous reaction).^{298,299}

Since many CDEs in the outpatient setting are unreported, studies that estimate the incidence of CDEs in the inpatient setting may under-report the occurrence of these conditions. The Boston Collaborative Drug Surveillance Program (BCDSP) captured some of the most comprehensive information available on CDEs. Therefore, studies of the BCDSP were used to estimate the prevalence of these conditions. The most currently available study, reported in 1991, estimated that 2.3 million individuals experience at least one CDE during the year.³⁰⁰ These estimates yield a prevalence rate of 900 cases per 100,000 individuals. Applying this to the 2004 U.S. population yields an estimate of 2.6 million individuals experiencing a CDE during the course of the year. The Compressed Mortality File did not attribute any deaths to CDEs in 2002.

Certain patient groups are at an increased risk for developing cutaneous drug eruptions, and even environmental factors, such as exposure to the sun, can alter patients' immune response to certain medications. Specifically, as the number and combinations of drugs taken by a patient increases, the potential for development of CDEs also increases. In women and patients of certain age groups (i.e., older patients, boys younger than 3 years, and girls older than 9 years) have an increased likelihood of experiencing CDEs.³⁰¹ Patients with viral infections (e.g., HIV, infectious mononucleosis, cytomegalovirus, and herpes virus) are also at increased risk of developing CDEs. Genetic predisposition likely plays a role in adverse cutaneous drug reactions, since genetic variation is tightly correlated with the metabolism of many drugs.

Direct Costs

The total direct costs associated with cutaneous drug eruptions is \$116 million (**Figure 8.4**). Of this total cost, physician office visits were responsible for nearly half at \$57 million for more than 767,100 visits. CDEs were listed as the primary diagnosis in 5,700 hospital admissions and implicated in more than 46,200 admissions for a total inpatient cost of \$20 million (**Figure 8.5**). Prescription drugs, at 19% of total costs, reflect the second largest cost component for treatment of CDEs at a cost of \$22 million. No cost information was available on OTC product expenditures for these conditions. Hospital outpatient departments and emergency rooms were used with relatively similar frequencies of at least 62,500 and 71,700 visits, respectively, for a combined cost of \$18 million.

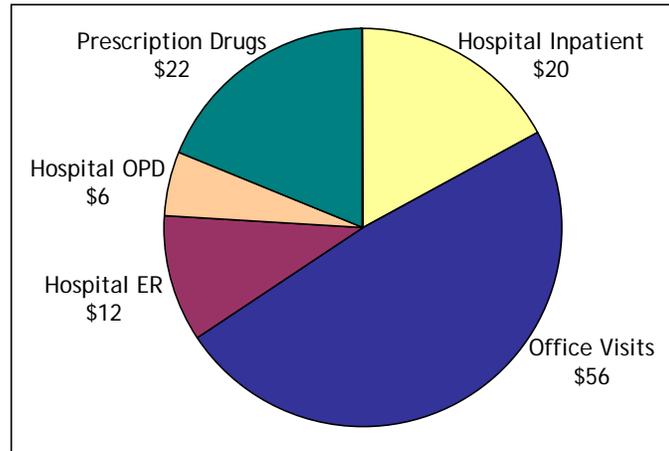
²⁹⁸ Nigen 2003.

²⁹⁹ Bachot 2003.

³⁰⁰ Levensen DE, Arndt KA, Stern RS. Cutaneous manifestations of adverse drug reactions. *Immunol Allergy Clin North Am* 1991;11:493-507.

³⁰¹ Nigen 2003.

Figure 8.4. Annual Direct Cost of Cutaneous Drug Eruptions, U.S.
(\$ millions, 2004)



Indirect Costs

Indirect costs associated with lost productivity due to CDEs are estimated at \$65 million (Figure 8.2). Due to a lack of age-specific prevalence data, further delineation into lost workdays, restricted activity days, and caregiver lost workdays was not feasible.

Intangible Costs Due to Quality of Life Impact

Even though the effects of CDEs on quality of life can range from mild to severe, a study quantifying these effects in the form of a DLQI score or a utility value could not be found in the literature. The limitations caused by these conditions must affect daily activities such as going to work and engaging in housework. Furthermore, their outwardly visible symptoms may hinder social interactions. A conservative estimate based on comparison of this condition to conditions with similar outward manifestations and effects on daily activities was made, resulting in an annual willingness-to-pay for symptom relief of \$12 million annually.

Figure 8.5. Health Care Utilization for Exogenous Skin Conditions

| Disease | Inpatient Hospital Stays | Inpatient Hospital Stays (primary diagnosis only) | Outpatient Hospital Visits | Emergency Room Visits | Physician Office Visits |
|--------------------------|--------------------------|------------------------------------------------------|----------------------------|-----------------------|-------------------------|
| Skin Ulcers and Wounds | 1,047,400 | 329,400 | 747,300 | 1,677,700 | 3,723,900 |
| Solar Radiation | 1,400 | 200 | 26,200 | 44,900 | 649,400 |
| Cutaneous Drug Eruptions | 46,200 | 5,700 | 62,500 | 71,700 | 767,100 |

Source: 2002-2003 NAMCS, NHAMCS, NHIS, NHDS adjusted to the 2004 US population

Chapter 9: Over-the-Counter Drug Costs for Skin Diseases

Costs of OTC drugs and other products relevant to the 21 skin disease categories considered in this study were derived primarily from 2003 data available from AC Nielson.³⁰² Other sources for OTC costs associated with psoriasis remedies and skin bleaching products were obtained from the literature, as cited in **Figure 9.1**. All costs were adjusted for inflation to 2004 U.S. dollars and adjusted to the 2004 U.S. population. Because of the manner by which OTC product sales are tracked and the lack of specific ICD-9 diagnostic/procedure codes associated with these purchases (as is the case with inpatient, outpatient and physician office procedures), it was not possible to reliably associate OTC spending with the individual disease categories in most cases. However, OTC costs are listed below for the categories of acne, psoriasis, solar radiation and certain cutaneous fungal infections (e.g., jock itch remedies), vitiligo (e.g., skin bleaching) and hair disorders (e.g., hair-growth products).

Figure 9.1 lists OTC costs by category, with a total OTC cost associated with these 21 skin disease categories estimated at \$2.1 billion in 2004. This total cost estimate is lower than the 2003 OTC estimate derived by Dehkharghani et al. (\$4.3 billion), in large part because that study (a) estimated the cost of a much larger complement of skin diseases (instead of a discrete set of disease categories) and (b) included a greater diversity of OTC products that may be relevant to that broader range of skin conditions (e.g., antiperspirants, feminine hygiene products, baby care products such as diaper rash treatments, first aid). Although some proportion of the broad spectrum of OTC costs cited in the 2003 Dehkharghani study are attributable to skin applications, many the categories included in that study were either not relevant or could not be concisely allocated to the 21 skin disease categories considered in this report.

³⁰² All costs in Figure 9.1, with the exception of those indicated with (* or **), reflect AC Nielson 2003 OTC sales by category data available from the Consumer Healthcare Products Association. Accessed February 1, 2005: http://www.chpa-info.org/web/press_room/statistics/otc_sales.aspx.

Figure 9.1. Over-the-Counter Drug Costs
(2004, U.S. dollars)

| Drug Category | Expenditures (millions) |
|------------------------------|----------------------------|
| Acne remedies | 312.1 |
| Foot preparations | 383.1 |
| Hair-growth products | 79.3 |
| Jock itch preparations | 42.8 |
| Lip remedies | 330.9 |
| Psoriasis remedies* | 472.1 |
| Sunscreen/sunburn | 319.4 |
| Skin bleaching** | 31.1 |
| Skin-cream - all purpose | 101.1 |
| Skin cream - special purpose | 41.0 |
| Total | 2,112.7 |

*Source: Javitz HS, et al. The direct costs of care for psoriasis and psoriatic arthritis in the United States. *J Am Acad Dermatol* 2002; 46(6):850-60.

**Source: Dehkharghani S. The economic burden of skin diseases in the United States. *J Am Acad Dermatol* 2003;48(4):592-9.

Because of the inability to reliably associate OTC costs with the 21 disease categories considered in this study, it is likely that the above numbers do not fully capture OTC spending, which is substantial and at times the largest cost component of certain skin disease expenditures (e.g., acne, psoriasis, solar radiation). Other categories, such as dermatitis, nail disorders, and cutaneous fungal infections, and some wounds (e.g., minor lacerations) are also anticipated to involve sizable OTC spending, since many individuals will attempt self-treatment for minor to moderate skin conditions prior to visiting a general practitioner or dermatologist.

Even when taking into account that some proportion of the OTC category costs above may be attributable to skin diseases outside of the 21 disease categories in this study, total OTC costs are likely underestimated. This is because certain OTC categories (e.g., first aid, baby care, antiseptics, petroleum jelly) relevant to these diseases could not be accurately associated with skin care for these categories. In other words, an unknown and potentially sizable proportion of OTC expenditures in such categories will apply to non-skin care applications (e.g., antiseptic cleaners for household and industrial sanitization, petroleum jelly use as a mechanical lubricant and rust preventative, baby care products that have non-skin care applications).

Targeted surveys may be the best available means of more accurately quantifying OTC costs associated with individual disease categories. When they have included a skin disease component, the large national surveys (e.g., NAMCS, NHAMCS) have not included questions that would capture sufficiently detailed OTC information by disease and product class to derive reliable, nationally representative estimates on OTC expenditures.