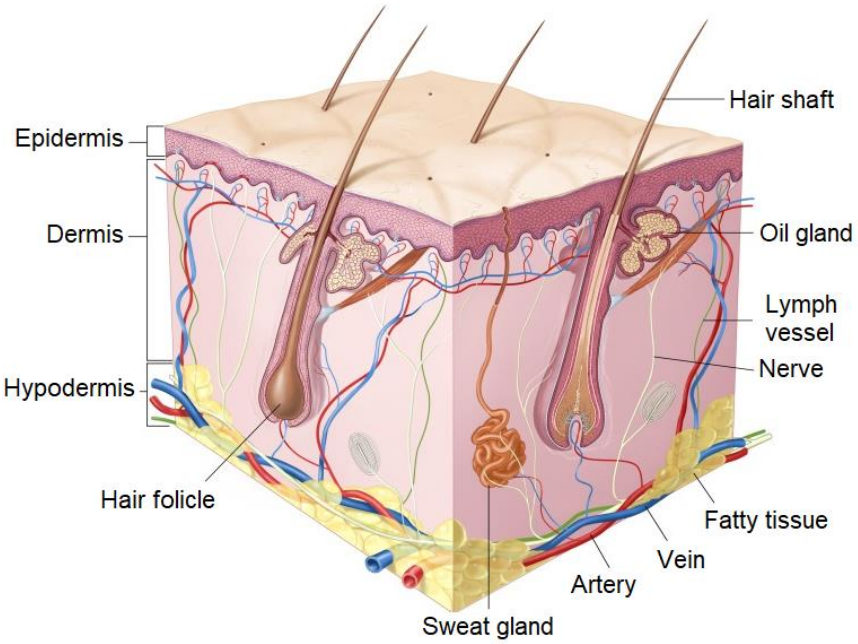
DERMATOLOGY TRAINING- READING MATERIAL

Contents

Skin

Skin is the second largest organ in the human body by surface area (following the small intestine). Skin pigmentation varies among populations (mostly due to geographic UV exposure), and skin type can vary with respect to dryness and the amount of oil. Likewise, the thickness as well as other properties of skin are different depending on the part of the body, age and sex.

Skin consists of three primary layers: **epidermis, dermis and hypodermis.** Epidermis is composed of tightly packed, interconnected layers of cells, while dermis and hypodermis are made of extracellular matrix, containing connective fibers, specialized structures, fat, nerves, circulatory vessels, and fewer cells.

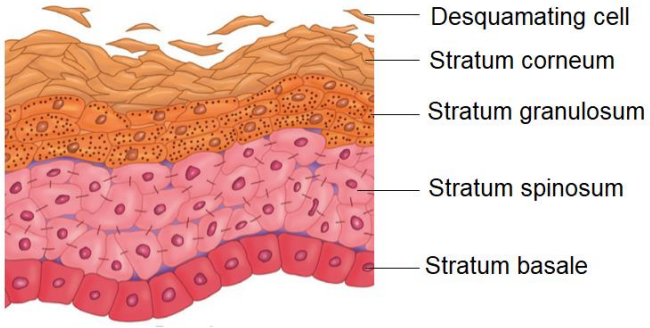


Anatomy of the skin

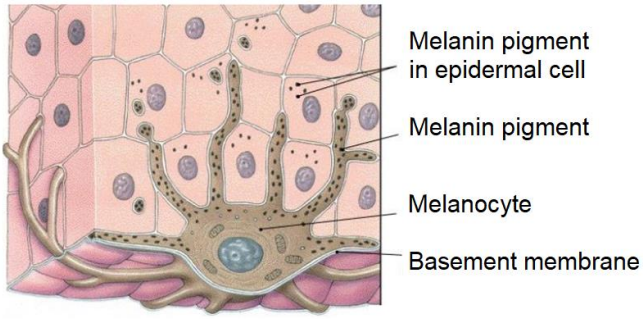
Skin is heavily populated with resident microbes of high diversity. Around 1000 bacterial species are present whose density and distribution varies according to the skin type at different body parts. Moist and sebaceous areas contain more bacteria than dry regions. Skin flora is usually harmless, although it can turn pathogenic and have negative effects, as in skin diseases or upon entering the bloodstream. There is a complex homeostatic relationship between skin and its microbes, and the functions of the resident microbiome are not entirely known.

Anatomy of the skin

Epidermis is the surface layer of the skin, itself composed of 5 sublayers. In the innermost sublayer (stratum basale) which itself lies on the basal lamina, new skin cells are created by mitosis. As these cells mature, they move up the layers, while differentiating, becoming enriched in keratin and flattening their shape, until they reach the surface layer (stratum corneum) and are desquamated (peeled off) in the environment. The lifespan of epidermal cells is around four weeks. Epidermis contains no blood vessels and is supplied via diffusion from capillaries underneath as well as oxygen from the exterior. Epidermal cells are tightly connected to each by specialized junctions, in other to provide a mechanical barrier against environmental insults. Apart from keratinocytes (epidermal skin cells), epidermis also contains several other types of cells. **Melanocytes** produce melanin, a dark pigment which protects against UV and gives skin its color. **Langerhans cells** are skin macrophages which perform immune functions, while **Merkel cells** have a function in touch sensation.



Layers of epidermis

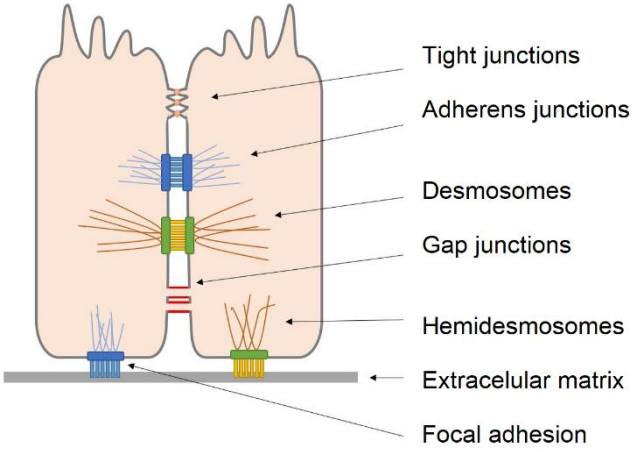


A melanocyte in epidermis

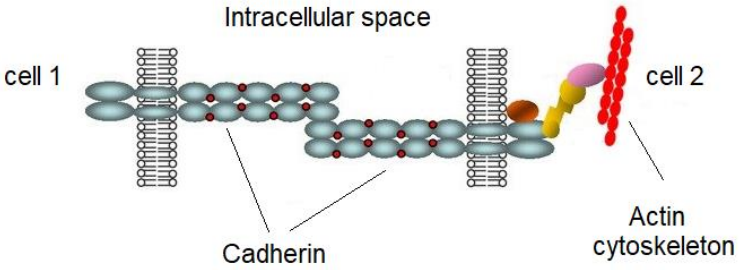
An important feature of epithelial cells is the manner in which they are interconnected, which is crucial to the structural and functional roles of epidermis and also partially enables communication among cells. The place of

attachment of two cells is called a **cell junction**, being composed of protein complexes (extending from each cell to establish mutual contact), which are linked to cytoskeleton toward the inside of the cell. There are several types of junctions and they are especially abundant in epithelial cells.

Tight junctions tightly seal the intercellular space, preventing leakage of fluids and transported solutes between cells. Immediately below are **adherens junctions**, which provide adhesion, as well as having more complex roles in cytoskeleton and intracellular signaling. **Desmosomes** are specialized for providing adhesion and resisting mechanical stress. Adherens junctions and desmosomes contain the same linker protein (cadherin) but on the inner surface of the cell connect to different cytoskeletal fibers. **Gap junctions** contain channels which connect cytoplasms of the two cells and allow direct passage of small molecules between them in a regulated way.

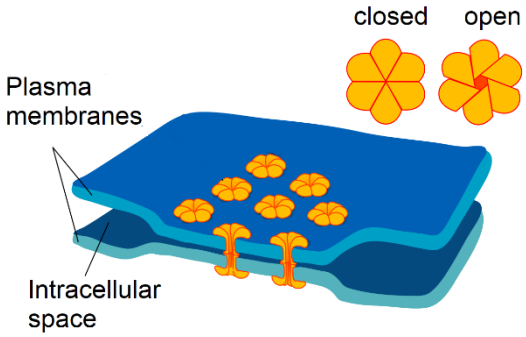


Types of junctions in epithelial cells



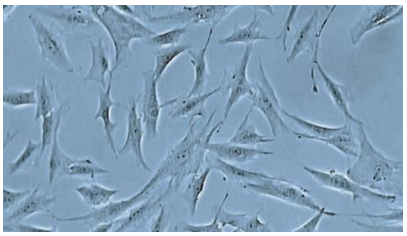
Cadherin proteins linking two cells (adherens junction)

Dermis is composed of extracellular matrix containing glycosaminoglycans, collagen, elastin, as well as hair follicles, sweat and oil glands, nerves, and blood and lymph vessels. The presence of glycosaminoglycans, which bind water, maintains turgidity of the skin, while collagen and elastin fibers provide skin with strength and elasticity. Apart from **fibroblasts**, cells which synthesize collagen and other fibers, dermis also contains **macrophages** and **mast cells** which have roles in immunity. Dermis is divided in **papillary dermis** and **reticular dermis**. Papillary dermis forms papillae (projections) into epidermis, providing nutrients to it. Reticular dermis is a thick and dense fiber-rich connective layer underneath papillary dermis. It provides skin with both strength and elasticity.

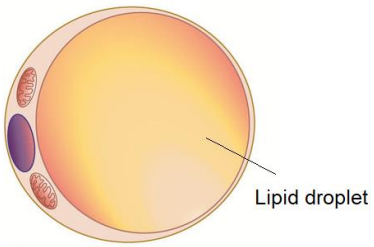


Gap junction

Hypodermis (subcutaneous tissue) is composed of loose connective tissue, which among other mentioned components and cells contains **adipocytes**, cells which store fat, which is linked to cushioning, thermoregulatory and energy reserve functions of skin.



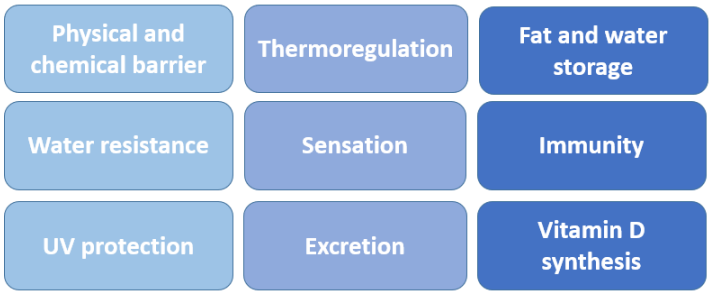
Fibroblasts in cell culture



An adipocyte in hypodermis with a fat reservoir (lipid droplet)

Functions of the skin

Rather than being a simple physical barrier toward external environment, skin performs a variety of functions. It provides mechanical and thermal insulation; thermoregulation is accomplished by controlling the diameter of blood vessels in response to outside temperature, as well as producing sweat. Skin (apart from stratum corneum) is impermeable to water, preventing fluid loss and minimizing evaporation. One of its main functions is sensory, as it is supplied with nerve endings reactive to pressure and changes in temperature. It is capable of excretion, for example through sweat, which contains urea and other substances. Skin also acts as a storage for fat, and it is the organ of vitamin D synthesis in response to UV light. Lastly, in addition to protecting from harmful UV radiation, it acts as a chemical and immunological barrier. It hosts specialized acids, lipids, immune components and other substances which prevent the passage of foreign chemicals and pathogens into the body.

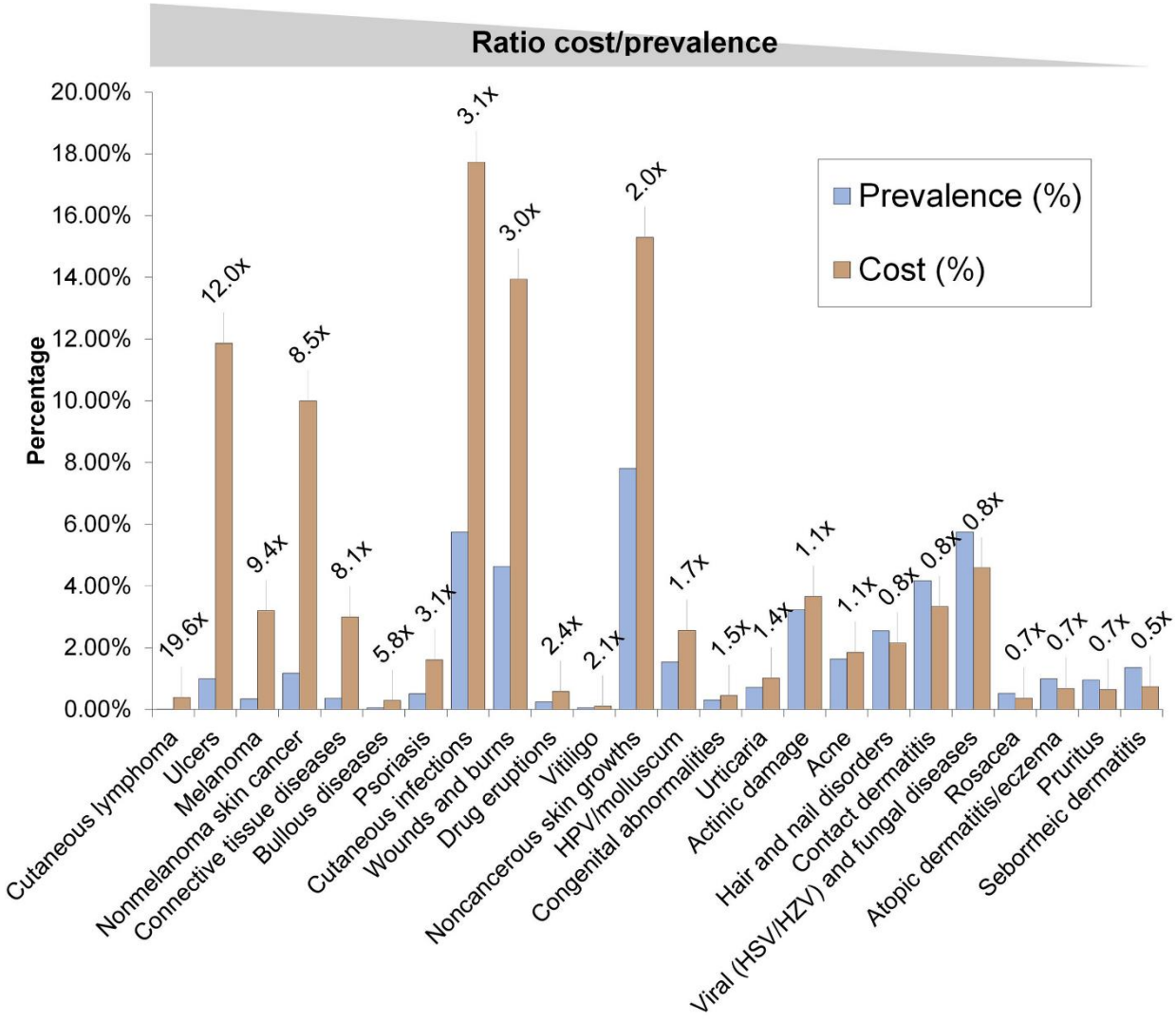


Skin functions

Skin conditions

Skin (cutaneous) conditions are some of the most common health problems with one in three people being affected at any time, making them more common than obesity, hypertension and cancer. There are more than 2,000 skin disorders of which only a small number accounts for most doctor visits. They are highly varied in their etiology, morphology, shape, color, permanence and distribution on the body. Some of them are associated with a severe impairment of the patients' quality of life. Skin conditions may be a result of infection by bacteria (cellulitis), viruses (herpes), fungi (athlete's foot) or parasites (scabies). Conditions such as acne or shingles are very common; on the other end of the spectrum, there are genetic skin disorders which are extremely rare, affecting only a few hundred people in the world. Skin cancers, psoriasis, and ulcers are comparatively uncommon but pose a very high healthcare and financial burden. In general, skin disease is one of the main contributors of disease burden worldwide; up to 25% of physician visits in the US are attributable to skin-related conditions.

Examples of rare skin diseases



Skin disease medical costs versus prevalence (2013, US). Comparatively rare conditions with high cost are on the left side of the chart. https://doi.org/10.1016/j.jaad.2016.12.043

Dermatology in clinical trials

Basic research and results from clinical trials have significantly improved the outcomes and quality of life of patients with dermatologic conditions. Underlying genetic components of many of these conditions have been uncovered, notably the BRAF oncogene mutations in malignant melanomas and polymorphisms associated with atopic dermatitis. The refinement of **lasers** has expanded their application in modern dermatology, since their initial use for tattoo removal. Currently, there is a rapid expansion of treatment options with the advancement of targeted therapies, precision and regenerative medicine. The use of **biologics** (drugs obtained or synthesized from living organisms) has greatly improved the management of psoriasis and other autoimmune conditions, while targeted immunotherapies have radically changed cancer treatment. As in other areas, the most important global trend is **personalized medicine,** which aims to 'provide the right treatment to the right patient, at the right dose, at the right time.' **Pharmacogenomics** investigates the role of the genome in drug response, with the goal of developing effective and safe drugs tailored to individual patient's genetic makeup.

A high share of dermatology clinical trials belongs to the development of treatments for skin cancer, psoriasis, eczema, ulcers and acne. COVID-19 has negatively affected the numbers of these trials, causing suspensions and terminations, and considerably reducing publication rates, while at the same time spurring innovation. For example, highly accurate **genomic testing** algorithms are used to process gene-expression data from skin biopsies and predict patient drug response, saving time and costs.

Out of around 17,000 currently active clinical trials globally, around 500 are in dermatology, involving 200,000 patients. Below are the numbers of trals for major dermatology indications. Incidentally, the global dermatology drug market is projected to grow from around $36 billion in 2020 to $40 billion in 2021.

Skin condition	Active clinical trials	Completed
Melanoma	271	1139
Psoriasis	82	1130
Atopic dermatitis (eczema)	42	594
Lupus Erythematosus	37	382
Leg Ulcer	29	452
Acne Vulgaris	16	473
Urticaria (Hives)	9	199
Herpes Simplex	8	177
Warts (genital, anal, oral, hand)	8	115
Pruritus (Itching)	7	288
Neurodermatitis	0	13
Scabies	0	19

Numbers of active clinical trials (not recruiting), as well as all historically completed trials, per skin condition. Clinicaltrials.gov, accessed March 2021.

Selected skin conditions and their assessment tools

Psoriasis

Psoriasis is a noncontagious autoimmune disease in which skin cells multiply up to 10 times faster than usual (every 3 to 4 days), producing areas of red bumps covered with white scales. These areas can be painful, itch and more rarely bleed, and usually appear on scalp, elbows or knees. They can heal and reappear throughout a person's life. Psoriasis typically starts in early adulthood and is long-lasting.

There are several different types, the most common being **plaque psoriasis (psoriasis vulgaris),** accounting for more than 80% of the cases. Other types include guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis. Different variants may coexist in one person at one time. The cause is unknown and likely multifactorial; stress, infections, medications and skin injuries appear to be main triggers. There is a clear genetic component and psoriasis has a tendency to run in families, skipping generations.

Psoriasis

The pathophysiology of psoriasis involves excessive **feed-forward activation of the adaptive immune system**, involving abundant cytokine secretion, differentiation of immune cells, and an inflammatory cascade, leading to disease manifestations: keratinocyte proliferation, increased expression of angiogenic mediators, and infiltration of immune cells.

There are various treatments which can be effective in controlling psoriasis symptoms. These include steroid creams aiming to suppress the immune system, UV phototherapy, or ointments aimed at moisturizing dry skin and relieving itching. The use of biologics is also recommended, specifically TNF-α and cytokine inhibitors. Although treatments can greatly diminish the symptoms, there is no cure. Around 2% of people are affected worldwide, and geographically it is most common in north Europe. Individuals with psoriasis experience substantial morbidity and increased rates of inflammatory arthritis and cardiometabolic diseases. Psoriasis is also often accompanied with depression, due to the patient's visual appearance.

Psoriasis affecting different areas

Assessment of psoriasis

The most frequent tools used for assessing psoriasis are **Psoriasis Area and Severity Index (PASI), Body surface area (BSA),** and **Physician's Global Assessment (PGA).** The impact of psoriasis on a patient's well-being is measured with **Dermatology Life Quality Index (DLQI).** Out of those, the dominant ones have been PASI and DLQI.

Psoriasis Area and Severity Index measures the body area affected by psoriasis, the extent of raised red patches, and the hardness and scaling of plaques**.** That is, firstly redness, thickness, and scaliness of the lesions are graded on a 0- 4 scale. Then, these scores are summed for each area of body affected (head, arms, trunk, legs). A percentage of skin affected in each area is expressed by a 0- 6 score, and then multiplied by the score for that area as well as by 0.1, 0.2, 0.3, and 0.4 for head, arms, trunk, and legs, respectively. By adding all of these together, a single score is finally calculated, which ranges from 0 (no psoriasis) to 72 (maximal psoriasis). One of the limitations of PASI is its poor sensitivity to change for small affected areas.

PASI

	Head	Arms
Area	○ 0% ○ <10% ○ 10-29% ○ 30-49% ○ 50-69% ○ 70-89% ○ 90-100%	○ 0% ○ <10% ○ 10-29% ○ 30-49% ○ 50-69% ○ 70-89% ○ 90-100%
Erythema (redness)	○ 0 ○ 1 ○ 2 ○ 3 ○ 4	○ 0 ○ 1 ○ 2 ○ 3 ○ 4
Induration (thickness)	○ 0 ○ 1 ○ 2 ○ 3 ○ 4	○ 0 ○ 1 ○ 2 ○ 3 ○ 4
Desquamation (scaling)	○ 0 ○ 1 ○ 2 ○ 3 ○ 4	○ 0 ○ 1 ○ 2 ○ 3 ○ 4
	Trunk	**Legs**
Area	○ 0% ○ <10% ○ 10-29% ○ 30-49% ○ 50-69% ○ 70-89% ○ 90-100%	○ 0% ○ <10% ○ 10-29% ○ 30-49% ○ 50-69% ○ 70-89% ○ 90-100%
Erythema (redness)	○ 0 ○ 1 ○ 2 ○ 3 ○ 4	○ 0 ○ 1 ○ 2 ○ 3 ○ 4
Induration (thickness)	○ 0 ○ 1 ○ 2 ○ 3 ○ 4	○ 0 ○ 1 ○ 2 ○ 3 ○ 4
Desquamation (scaling)	○ 0 ○ 1 ○ 2 ○ 3 ○ 4	○ 0 ○ 1 ○ 2 ○ 3 ○ 4

Dermatology Life Quality Index is a simple questionnaire consisting of 10 questions, each of which contributes up to 3 points toward a total of 30 (maximum impact on quality of life). It addresses topics such as symptoms, embarrassment, shopping, clothes, work, sport and social life. It is not psoriasis specific, but has been used widely in psoriasis trials and for patient monitoring.

Excerpt from the DLQA

4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much ❒ A lot ❒ A little ❒ Not at all ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much ❒ A lot ❒ A little ❒ Not at all ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much ❒ A lot ❒ A little ❒ Not at all ❒

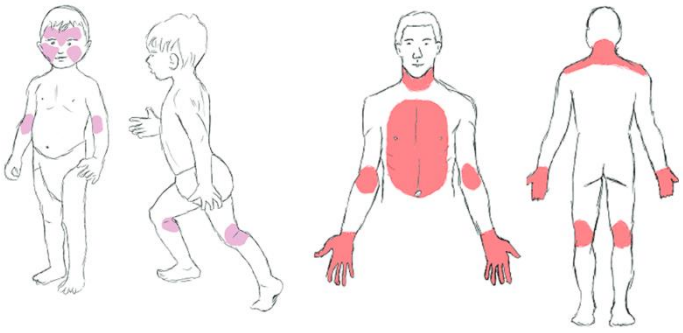
Body surface area measures the total area of body affected by psoriasis and classifies the severity of the condition based on the percentage of that area. **Physician's Global Assessment** is a 5-, 6-, or 7-point scale (usually 7) that classifies psoriasis as clear, nearly clear, mild, moderate, severe, or very severe, with each of those corresponding to a specific definition.

Dermatitis

Dermatitis (also known as eczema) is inflammation of the skin, usually characterized by dryness, itchiness, redness, swelling and a rash. There are different types of dermatitis and symptoms as well as the skin area affected vary according to the type; bumps, blisters and scarring may also appear. **Atopic dermatitis** is the most common type; others are **contact dermatitis (allergic and irritant), seborrheic dermatitis** and **stasis dermatitis**. Similarities in the clinical presentation of different types of dermatitis often create a challenge for healthcare providers in terms of adequate treatment. The precise cause of dermatitis is unknown; both genetic and environmental factors are important as well as immunal dysregulation; different environmental triggers are relevant depending on the person. Treatment of dermatitis among others involves moisturizing creams, corticosteroids, and irritant/allergen avoidance.

Atopic dermatitis (AD) most frequently occurs in childhood and it is estimated to affect up to 20% of children and 3% of adults worldwide. It may persist chronically or come and go throughout an individual's lifetime. Pathophysiology involves a complex interplay among epidermal barrier dysfunction, immune dysregulation, and environment. Body areas affected by AD can vary by patient age; in children forehead and cheeks are most often involved and in adults face, neck, chest and flexural surfaces become more common. Individuals with AD are also at risk of developing asthma, allergic rhino conjunctivitis, food allergies and secondary infections.

Atopic dermatitis



Areas affected by atopic dermatitis in children and adults

Contact dermatitis is the most common occupation-associated skin condition, with the irritant type accounting for 80% of cases. **Allergic contact dermatitis** occurs in response to an allergen and the **irritant** type is caused by various physical and chemical irritants. Irritant type is especially associated with occupations in the manufacturing industry, arts, food services and health care provision, because of hygiene practices. **Seborrheic dermatitis** is a long-term condition which affects areas rich in oil-producing glands such as face and scalp. **Stasis dermatitis** affects legs and is associated with low venous return and varicose veins.

Assessment of dermatitis

A large number of assessment tools have been used for the treatment of dermatitis. The most commonly used in atopic dermatitis are **Scoring atopic dermatitis, Investigator Global Assessment, and Eczema Area and Severity Index.** Eczema Area and Severity Index (EASI) has emerged as the preferred tool in clinical trials. It takes into account four symptoms- erythema, edema/papulation, excoriation (appearance of lesions from skin picking), and lichenification (skin becoming thick and hardened). First, the extent of eczema (area affected) is assessed separately for each body part and scored on a 0- 6 scale. Next, the severity of each of the four symptoms is scored on a 0- 3 scale. Symptom scores per body part are added up, multiplied by its area score as well as its multiplication factor, and lastly all the individual body part scores are added to arrive at a single final EASI score (0-72).

EASI

Area of Involvement:

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

Severity of Signs:

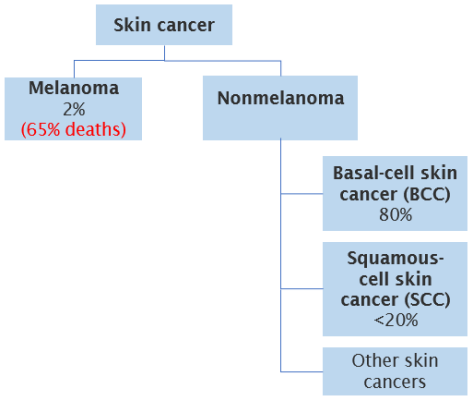
0	None
1	Mild
2	Moderate
3	Severe

Scoring table:

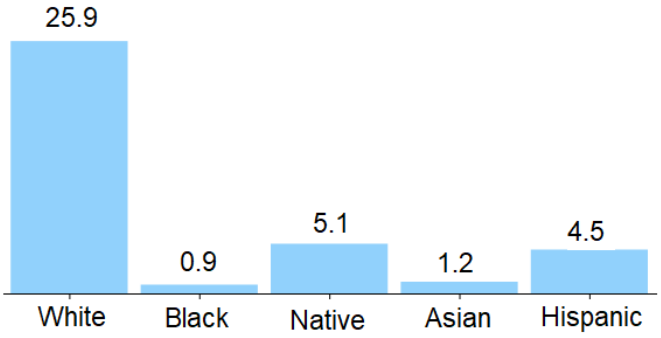
Body region	Erythema	Edema/ papulation	Excoriation	Lichenification	Area score	Multiplier	Score
Head/neck	(+	+	+	)	x	x 0.1	
Trunk	(+	+	+	)	x	x 0.3	
Upper extremities	(+	+	+	)	x	x 0.2	
Lower extremities	(+	+	+	)	x	x 0.4	
The final EASI score is the sum of the 4 region scores							——— (0-72)

Skin cancer

Skin cancer is the most common type of cancer worldwide. Countries with the highest incidence are Australia and New Zeeland, with Northern Europe also having high rates. Epidemiology is heavily dependent on the race (skin color). It develops mainly on areas of skin exposed to sun, including the face, scalp, chest, arms and hands. The most frequent types of skin cancers are **basal cell carcinoma (BCC)** and **squamous cell carcinoma (SCC)**, which are nonmelanoma types. **Melanoma** it accounts for only 2% of all skin cancers but causes most skin cancer deaths (65%). Death from basal and squamous cell skin cancers is uncommon and mostly related to the elderly who have not seen a doctor until the cancer had become large. Both melanoma and nonmelanoma cases are rapidly rising worldwide, but show a stable or decreasing mortality rate. There are also several other less common types of skin cancer.



Major types of skin cancer



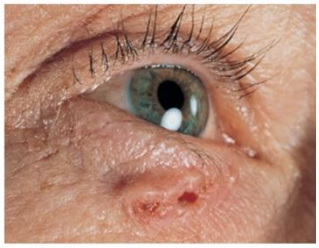
Melanoma rate in the US per 100,000 people by race, CDC. https://gis.cdc.gov/Cancer/USCS/DataViz.html

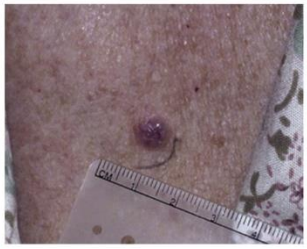
Males				Females		
Prostate	248,530	26%		Breast	281,550	30%
Lung & bronchus	119,100	12%		Lung & bronchus	116,660	13%
Colon & rectum	79,520	8%		Colon & rectum	69,980	8%
Urinary bladder	64,280	7%		Uterine corpus	66,570	7%
Melanoma of the skin	62,260	6%		Melanoma of the skin	43,850	5%
Kidney & renal pelvis	48,780	5%		Non-Hodgkin lymphoma	35,930	4%
Non-Hodgkin lymphoma	45,630	5%		Thyroid	32,130	3%
Oral cavity & pharynx	38,800	4%		Pancreas	28,480	3%
Leukemia	35,530	4%		Kidney & renal pelvis	27,300	3%
Pancreas	31,950	3%		Leukemia	25,560	3%
All Sites	**970,250**	**100%**		**All Sites**	**927,910**	**100%**

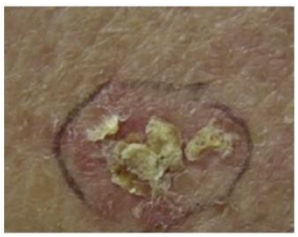
Estimated numbers of cases for melanoma and other most common cancers for 2021 (American Cancer Society). Incidence data are not collected for basal cell and squamous cell skin cancers (note that including those, skin cancer accounts for 40% of all cancers). https://doi.org/10.3322/caac.21654

BCC is derived from the basal cells; it is the most common and least deadly form, usually slow growing and easily treated with surgery or radiation. It appears in the form of a small papule that may enlarge slowly over months or years, developing a central ulcer, with common bleeding. It is often mistaken by patients as a pimple. Metastasis is rare, but local growth can be very destructive.

SCC is the second most common form of nonmelanoma skin cancer. It is a malignant tumor of epidermal keratinocytes that invades the dermis. Clinical manifestations include papules, plaques, or nodules, and smooth, crusty or erosive lesions. Bleeding may occur; eventually, the tumor ulcerates and invades the underlying tissue. It metastasizes more often than BCC but still relatively rarely compared to melanoma. If small SCC lesions are removed early, the prognosis is very good.

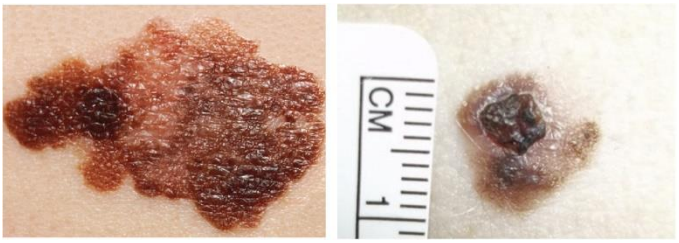




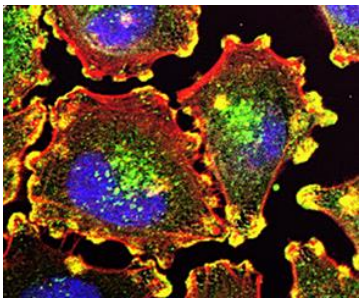


Basal cell carcinoma *Squamous cell carcinoma*

Melanoma develops from melanocytes; individuals with fair (pale) skin and chronic sun exposure are at the highest risk for melanoma; it is 20 times more common for people of white than black race (also much less common for Asians and Hispanics). Around 25% of melanomas develop from moles; a mole starts to change its size, shape or color, showing an irregular border. It usually arises on the skin surface and is therefore detectable by visual examination. Metastatic melanoma tends to spread to brain, liver, bones, lymph nodes and abdomen. The primary treatment of melanoma is surgical removal; additional options are immunotherapy, targeted drug therapy, chemotherapy and radiation.



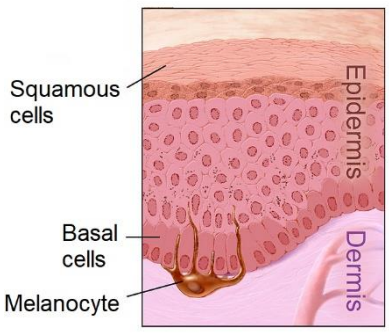
Melanoma



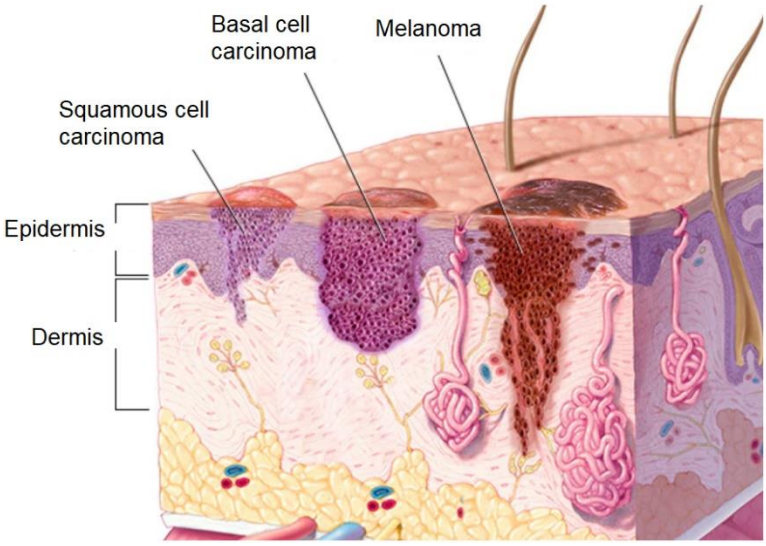
Motility of melanoma cells- podosomes (yellow) contain highly concentrated actin fibers (red) allowing the cells to migrate, invade neighboring tissue, and spread metastatically

The pathogenesis of skin cancer is multifactorial, with UV light from sunlight being the main cause. UV light produces DNA damage, gene mutations, immunosuppression, oxidative stress, and inflammatory responses, all of which contribute to skin cancerogenesis. The two main types of UV light are UVA and UVB. While UVB rays directly damage DNA, the damage to DNA from UVA rays is indirect, mediated by free radical formation and effects on cellular membranes.

Since **vemurafenib** (BRAF-targeted inhibitor) received FDA approval in 2011 for the treatment of melanoma, targeted therapy and immunotherapy have become the new standards of care, substantially improving survival rates.



Cells producing main types of skin cancer



Main types of skin cance

Assessment of melanoma

The universal standard for classifying the spread of tumor is the **TNM staging system.** It is also referred to as the **AJCC system** (American Joint Committee on Cancer), currently in its 8th edition. The revisions of the melanoma staging system over time reflect changes in the understanding of this tumor's biology, and they incorporate new clinicopathological factors. Future prospects include the use of new analytics and molecular data to personalize prognostic information.

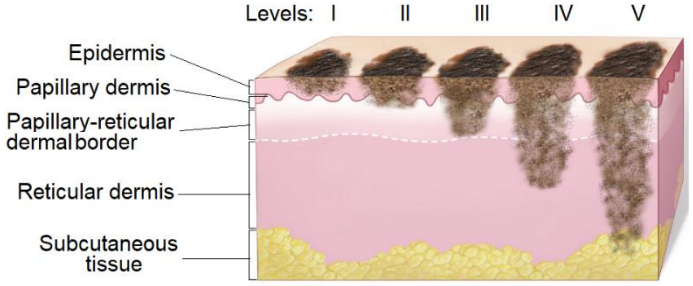
T (tumor) describes the size of the primary tumor (thickness) and invasion of nearby tissue; N (node) describes the involvement of nearby lymph nodes; M (metastasis) relates to the existence of distant metastasis. For example, in case of melanoma, T4b would mean it is thicker than 4mm and with ulceration, N1 would that it is found in one lymph node, and M1b stands for metastasis to lung. Ulceration is a breakdown of the skin on top of the melanoma, which poses a greater risk for spreading. After TNM categories are identified, the overall stage number is assigned, with a lower stage number signifying less advanced tumor progression.

Apart for this, **Clark's level** and **Breslow's depth** have also been used in conjunction for melanoma, and refer solely to tumor depth (anatomical invasion). Clark's level is less reproducible and has a lower predictive value than Breslow depth. It comprises five levels, while Breslow's depth is divided in five stages.

M Category	Anatomic Site	LDH Level
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	
M1a	Distant metastasis to skin, soft tissue including muscles, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated

AJCC 8th edition M category (distant metastasis) criteria. LDH is lactate dehydrogenase. Doi: 10.1080/14737140.2018.1489246

Level 1	Melanoma confined to the epidermis
Level 2	Invasion into papillary dermis
Level 3	Invasion to the border of papillary and reticular dermis
Level 4	Invasion into the reticular dermis
Level 5	Invasion into the subcutaneous fat



Clark's level

Stage	Depth
I	0.75 mm or less
II	0.76 mm - 1.50 mm
III	1.51 mm - 4.00 mm
IV	>4 mm

Breslow's depth

Melanoma in situ (stage 0, or Tis) according to the TNM system, contained within epidermis

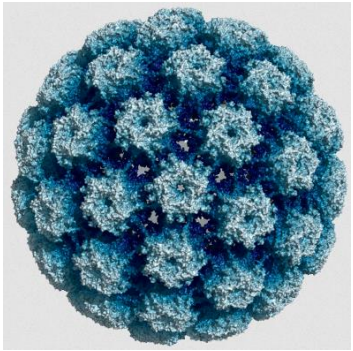
Conditions associated with human papillomavirus

Papillomaviruses are small circular double-stranded DNA viruses. They are highly species-specific and preferentially infect cutaneous or mucocutaneous epithelium. There are more than 200 HPV genotypes, out of which over 160 have been sequenced. They are spread through skin-to-skin contact and around 40 types are spread sexually. Many of these are harmless, while twelve HPVs are defined as being high-risk cancer causing types, most important of those being 16 and 18.

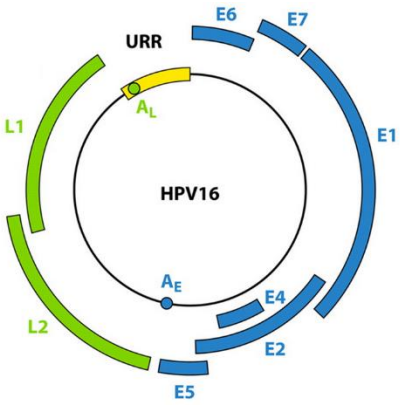
HPV causes **warts** and lesions which may lead to **cancer**, in various areas of the body. During evolution, HPVs have adapted to specific epithelial niches, with different types having different disease associations and prevalence. Conversely, they can also be grouped according to the areas of the body where infection is found- external skin, anogenital and oral regions.

Disease		Most frequently associated HPV types
Common warts		HPV 2,4,7; occasionally others
Flat plane warts		HPV 3,10, occasionally HPV 26–29 and 41
Plantar warts		HPV 1,2,4
Epidermodysplasia verruciformis*	Plane warts	HPV 3,10
Anogenital warts*	External warts	HPV 6,11,40,42,43,44,54,61,72,81,89
Anogenital cancers and precancers	Group 1: carcinogenic to humans (there are two additional groups)	HPV 16,18,31,33,45,51,52
Oral lesions*	Oral papillomas	HPV 2,6,7,11,16,18,32,57
	Oropharyngeal carcinoma	HPV 16 predominantly,18

HPV types associated with particular diseases. Asterisk indicates the existence of additional clinical manifestations of the condition, which may correspond to different HPV types.



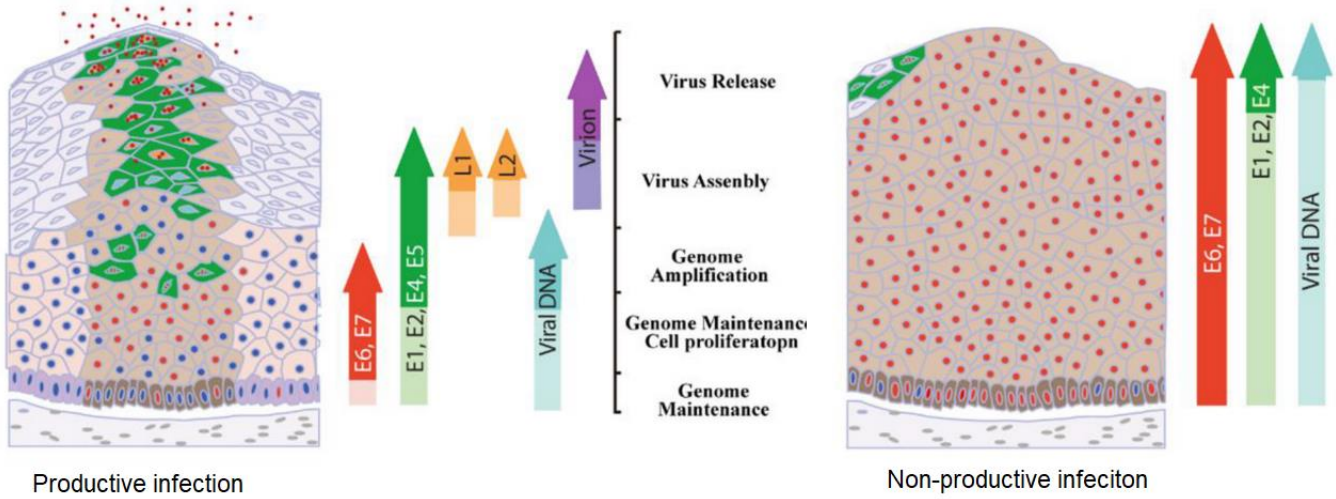
Cryo-electron microscopy of the HPV16 capsid



HPV16 genome organization

HPV infects basal epithelial cells of skin and mucosa, usually through surface skin micro wounds. It produces viral particles in matured epithelial cells and then causes a disruption in normal cell cycle control, the promotion of uncontrolled cell division and the accumulation of genetic damage. HPV genome is small, and the virus largely relies on the hijacked cellular machinery for its replication. After amplification of viral DNA, the next steps (in the productive phase) are the expression of the remaining viral genes, encapsidation of viral DNA, and the release of newly formed infectious virions. Tumor progression is especially characterized by the increased expression of HPV genes that inactivate p53 and pRb, integration of viral DNA into host genome, and alterations of key cell cycle regulators.

HPV infection can be **productive, subclinical** or **latent. Productive** infections are associated with full viral gene expression and production of mature virus particles. Productive lesions such as warts can be seen clinically, while **subclinical** mucosal infections require microscopic examination. **Latent** papillomaviruses can only be detected by the presence of HPV DNA within normal skin, typically by PCR. Around 90% of HPV infections resolve spontaneously within the first two years, which requires an efficient immune response. On the other hand, a persistent infection with high-risk types increases the risk of progression to cancer.



Expression of HPV genes in a productive vs. non-productive infection

There are nongenital and genital **warts**. Warts are benign lesions, with hypertrophy of all layers of the dermis, resulting in thickening, folding and hyperkeratosis. Warts usually disappear spontaneously; regrowth of lesions after treatment is frequently due to persistence of the virus in the skin surrounding the original wart. **Nongenital warts** include **common warts** (most often on the hands), **flat warts** (on the backs of hands and legs), and **plantar warts** (on the soles of the feet). **Nongenital warts** in immunocompetent people are harmless and usually resolve spontaneously. **Common warts** are usually exophytic, multiple, irregular, rough nodules which show a variety of clinical patterns at different sites of trauma, particularly on fingers. **Flat warts** are small and less rough, presenting as flat-topped papules, flesh colored or lightly pigmented, especially on light exposed areas. **Plantar warts** arise most frequently through barefoot activities. Activities which cause maceration of the skin such as swimming provide an additional risk of transmission. Infected keratinocytes are shed onto abrasive surfaces such as diving boards or swimming pool surroundings, thus spreading virus to the feet of other swimmers.

Anogenital warts are caused mostly by low-risk HPV types 6 and 11. These infections are more common than those that cause nongenital warts, and the majority are asymptomatic. HPV is present in 50-80% of sexually active young men and women, and external genital warts (condylomata acuminata) are the most common sexually transmitted infection. They may occur as small papular or large cauliflower-like lesions on moist surfaces, or as keratotic lesions resembling skin warts on dry areas. They vary in color, with many being too small to be seen without magnification. Transmission requires close contact, which is not necessarily sex, and can even easily happen for example through sharing baths or towels. An important mode of HPV spread is also vertical transmission of HPV from mother to infant, either in utero or during delivery.

Warts are often treated surgically, with cryotherapy, drugs, acid treatments and laser; most recently, green tea extract has shown promising results in clinical trials.

Common warts, flat warts on the face, and plantar warts

Most HPV infections clear spontaneously but persistent infection with the oncogenic or high-risk types may cause cancer. **Cervical cancer** is by far the most common HPV-related cancer and HPV is currently the second most common cause of cancer-related deaths in women worldwide (after breast cancer). There are three main vaccines against HPV; all prevent infection with high-risk types 16 and 18, which cause about 70% of cervical cancers. Apart from cervical cancer, HPV is responsible for a large proportion of anal, penile, vaginal, vulval, and oropharyngeal cancers.

The range of infections, precancers and malignancies associated with HPV continues to grow. While much effort worldwide focusses on the potential to eradicate cervical cancer by HPV vaccination programs targeting pre-sexually active girls, the burden of disease is increasing for other cancers as well. HPVs remain both highly effective pathogens and carcinogens, well adapted to their ecological niches, and capable of avoiding immune responses.

Assessment of warts in clinical trials

Assessment of warts in clinical trials usually relates simply to the frequency of complete clearance of warts at follow-up, frequency of reduction in number and/or size of warts, or the duration of the response. Sometimes, the effect of treatment is evaluated on a single wart per patient in a large patient group, or two warts in a single patient may receive alternative treatments. More recently, digital photography has been used to record warts and track their changes more accurately. Modifications of Physician's Global Assessment and Patient's Global Assessment may also be used solely or in concert, as well as various patient questionnaires.