Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet
on
Erythroplakia

Introduction

Erythroplakia (or erythroplasia) is a clinical term to describe any erythematous (red) area on a mucous membrane that cannot be attributed to any other pathology (illness condition).

[Picture Credit: Erythroplakia]

The term erythroplasia was coined by Louis Queyrat to describe a precancerous red lesion of the penis. This gave rise to the term erythroplasia or Querat. Depending upon the context, this term may refer specifically to carcinoma *in situ* of the glans penis or vulva appearing as a red patch, or may be used as a synonym of erythroplasia on other mucous membrane or transitional sites. It mainly effects the glans penis (the head of the penis), although uncommonly it may present on the mucous membranes of the larynx, and rarely, the mouth, or the anus.
(Wikipedia).

Complications of Erythroplakia

The list of complications that have been mentioned in various sources for Erythroplakia (erythroplasia) includes:

- Tongue abnormality
- Mouth or peri-oral changes
- White lesions on the mucosa of the mouth
- Carcinogenesis (the development or growth of cancer).

(Right Diagnosis).

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Incidence of Cancer of the Mouth in South Africa

The National Cancer Registry (2012) does not provide any information regarding the incidence of Erythroplakia in South Africa.

According to the National Cancer Registry (2012) the following number of cancer of the mouth cases was histologically diagnosed in South Africa during 2012:

Group - Males 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	406	1:346	1,10%
Asian males	16	1:331	1,87%
Black males	217	1:423	1,86%
Coloured males	59	1:227	1,35%
White males	114	1:256	0,57%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	198	1:1 009	0,53%
Asian females	12	1:637	1,10%
Black females	75	1:2 080	0,45%
Coloured females	40	1:338	0,96%
White females	71	1:542	0,45%

The frequency of histologically diagnosed cases of cancer of the mouth in South Africa for 2012 was as follows (National Cancer Registry, 2012):

Group - Males 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	1	4	9	53	125	198	62	16
Asian males	0	1	0	1	3	5	1	2
Black males	1	3	7	21	74	58	29	6
Coloured males	0	0	0	11	13	20	7	4
White males	0	0	2	13	32	36	21	4

Group - Females 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	3	1	6	13	46	58	38	29
Asian females	0	0	0	0	2	5	2	1
Black females	1	1	3	8	14	16	11	13
Coloured females	0	0	0	0	13	16	7	1
White females	1	0	3	3	13	17	16	10

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Signs and Symptoms of Erythroplakia

Precancerous conditions of the oral cavity have the potential to develop into oral cavity cancer. When cells that line the oral cavity are exposed to carcinogens, such as cigarette smoke, they can change and become more likely to develop into cancer (this process is known as field cancerisation). The affected area may have visible precancerous lesions (abnormal areas), but precancerous conditions are often not apparent. As a result, precancerous or cancerous conditions may appear later, even after abnormal areas are treated.

The most common precancerous conditions of the oral cavity are:

- leukoplakia

- erythroplakia
- erythroleukoplakia
- proliferative verrucous leukoplakia (PVL)
- oral submucous fibrosis

The signs and symptoms of leukoplakia may include a whitish area or spots inside the mouth that cannot be easily scraped off.
(Canadian Cancer Society).

Differential diagnosis
The following conditions should be considered before making a diagnosis of erythroplakia:

- Non-homogeneous leukoplakia
- Erosive lichen planus
- Acute atrophic candidiasis
- Invasive oral cancer
- Pemphigus
- Lupus erythematosus
- Denture induced stomatitis
- Haemangioma

(IARC Screening Group).

Risk Factors for Leukoplakia
The following risk factors may increase a person's chance of developing leukoplakia:

- heavy smoking
- excessive alcohol use
- chewing tobacco

(Canadian Cancer Society).

Diagnosis of Leukoplakia
Erythroplakia is seldom multicentric (having multiple centres of origin) and rarely covers extensive areas of the mouth. It is soft on palpation and does not become indurated (hardened) until an invasive carcinoma (malignancy) develops in it. It is often asymptomatic (without symptoms), although some patients may complain of a sore, burning or metallic sensation. Oral erythroplakia has the highest risk of malignant transformation compared to all other mucosal lesions. Histological examination of clinically diagnosed erythroplakia often shows severe epithelial dysplasia, carcinoma *in-situ* or micro-invasive cancer.

All erythroplakias should be viewed with extreme clinical suspicion for malignancy, as they are more likely to harbour histological foci of severe dysplasia, carcinoma *in-situ* (CIS) or invasive cancer. We advise excision biopsy and histological examination as a mandatory procedure whenever an erythroplakia is clinically diagnosed.
(IARC Screening Group).

Treatment of Leukoplakia

Surgical excision - which can be accomplished with a scalpel or a CO2 laser, is the treatment of choice for epithelial dysplasia of the oral cavity. The laser provides a relatively bloodless surgical field and in one report actually reduced recurrences. To date neither technique has been shown to be better than the other in preventing recurrence.

Once an incisional biopsy has established the diagnosis of epithelial dysplasia, the remainder of the lesion should be removed completely, as the probability of malignant change, although unknown, must be considered substantial. Reported recurrence rates for premalignant lesions are as high as 34.4%. One study found an 18% recurrence rate in cases of severe epithelial dysplasia or carcinoma *in situ* in which the lesion had been excised with a 3-5mm margin of normal tissue. Whether recurrence relates to continued exposure to risk factors or to an underlying mechanism that initiated the original lesion is unclear, but patients should be closely monitored for recurrence regardless.

The hyperkeratotic lesion is difficult to manage because it has potential for malignant change but is not yet considered dysplastic. As a first step, the clinician should remove any local irritants. If after 2 weeks the hyperkeratosis is still present, excision should be considered, especially if the lesion is in a high-risk site (e.g., floor of mouth and ventral tongue) or if the patient has been exposed to established risk factors for oral cancer.

Chemoprevention - If the size of the lesion, its location, or the medical status of the patient would make surgical removal difficult, use of antioxidant supplements should be considered as 'chemoprevention' to try to prevent progression to carcinoma. Beta-carotene and the retinoids are the most commonly used antioxidant supplements for chemoprevention of oral cancer. However, although antioxidant supplements have shown promise, they have an uncertain success rate and no long-term results. Still, antioxidant supplementation may be appropriate if there is recurrence after surgical excision but concern that a second excision would not prevent another recurrence. Patients with leukoplakia involving a large area of the oral mucosa might also be candidates for antioxidants, as might patients with extensive medical problems that increase their surgical risk.

Beta-carotene is a carotenoid found primarily in dark green, orange, or yellow vegetables. Several clinical trials have found that treating oral leukoplakia solely with beta-carotene supplements is associated with clinical improvement; rates have ranged from 14.8% to 71%.

No side effects have been reported in patients given beta-carotene supplements; but there is little information about recurrence following discontinuation of this substance. Retinoids are compounds consisting of natural forms or synthetic analogues of retinol. Of the more than 1 500 synthetic analogues of vitamin A, 13-cis-retinoic acid (13-cRA), also known as isotretinoin or Accutane®, has generated the most interest. 13-cRA has been shown to cause temporary remission of oral leukoplakia, but it also causes side effects in a high percentage of patients.

A study at M.D. Anderson Hospital in Houston followed 44 patients with oral leukoplakias who were treated with 1-2 mg/kg/day of 13-cRA for 3 months; nearly 67% of the patients had more than a 50% reduction in lesion size, but 79% experienced a variety of side effects. Other studies have noted that lowering the 13-cRA dose reduced the incidence and severity of side effects, but there have been numerous reports of recurrence after discontinuation. A rise in serum triglycerides has also been reported with use of 13-cRA.

To date, no combination of antioxidants has demonstrated its clear superiority. Beta-

carotene with ascorbic acid and/or alpha tocopherol is attractive because of a lack of side effects, but clinical improvement typically takes several months. 13-cRA requires a shorter time to produce a clinical response, but use of this substance necessitates baseline and periodic serologies and close monitoring.
(The Oral Cancer Foundation).

About Clinical Trials
Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials
Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in

writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for

a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or "trial arms": (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.
In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

<u>Use of Placebos</u>

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the

study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

Whilst CANSA has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

Sources and References

Canadian Cancer Society
http://www.cancer.ca/en/cancer-information/cancer-type/oral/oral-cancer/precancerous-conditions/?region=on

Erythroplakia
http://burketsoralmedicine.blogspot.com/2012/12/erythroplakia.html

IARC Screening Group
http://screening.iarc.fr/atlasoral_list.php?cat=A3&lang=1

National Cancer Institute
http://www.cancer.gov/clinicaltrials/learningabout/what-are-clinical-trials
http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials

Right Diagnosis
http://www.rightdiagnosis.com/medical/mouth_and_perioral_signs.htm

The Oral Cancer Foundation
http://www.oralcancerfoundation.org/cdc/cdc_chapter4.php

Wikipedia
http://en.wikipedia.org/wiki/Erythroplakia