ENVIRONMENTAL FACTORS IN VIRUS-ASSOCIATED HUMAN CANCERS

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KEY FACTS ABOUT CANCER

- Cancer is a leading cause of death worldwide.
  - 7.6 million deaths (~13% of all deaths) in 2008;
  - Estimated 13.1 million deaths by 2030.
- Development of cancer is a multistage process resulted from the interaction between a person's genetic factors and external carcinogens, such as infections from certain viruses.

- Viral infections have been found to contribute to 15-20% of all human cancers.
- Seven oncogenic viruses
  - DNA viruses: Epstein-Barr virus (EBV), Hepatitis B virus (HBV), Human herpes virus-8 (HHV-8), Human papillomavirus (HPV) and Merkel cell polyomavirus (MCPyV)
  - RNA viruses: Hepatitis C virus (HCV) and Human T lymphotrophic virus-1 (HTLV-1)

Oncogenic Viruses	Associated Cancer Types
Epstein-Barr virus (EBV)	Burkitt's lymphoma, Hodgkin's lymphoma and Nasopharyngeal carcinoma
Human T lymphotrophic virus-1 (HTLV-1)	T-cell leukemia
Merkel cell polyomavirus (MCPyV)	Merkel cell carcinoma

- ✓ Viral infection alone usually does NOT lead to cancer.
- ✓ Certain risk factors, such as aging, genetic factors and environmental factors, appear to be involved in the viral oncogenesis.

ENVIRONMENTAL RISK FACTORS

- It is generally accepted that about 80% of all cancers have an environmental component.
- "Environmental factors"
  - Individual's personal environment, which includes lifestyle choices such as diet, tobacco use and alcohol abuse;
  - External environmental causes, which refer to factors in the environment such as environmental pollutants.

Oncogenic Viruses	Associated Cancer Types	Environmental Cofactors
EBV	Burkitt's lymphoma	Chemotherapy and co-infection with HIV
	Hodgkin's lymphoma	Co-infection with HIV
	Nasopharyngeal carcinoma	Formaldehyde, wood dust, salted fish (Chinese style) and tobacco smoking
HBV	Hepatocellular carcinoma	Aflatoxins, alcoholic beverages, oral contraceptives, tobacco smoking and vinyl chloride
HCV		
HHV-8	Kaposi's sarcoma	Co-infection with HIV
HPV	Cancers of cervix, anus, penis, vagina and vulva	Diethylstilbestrol, oral contraceptives, tobacco smoking and co-infection with HIV
	Some cancers of the head and neck	Alcoholic beverages; betel quid with/without tobacco and tobacco smoking
HTLV-1	T-cell leukemia	Benzene, formaldehyde, chemotherapy, ionizing radiation and co-infection with HIV
MCPyV	Merkel cell carcinoma	Ultraviolet radiation and co-infection with HIV

ENVIRONMENTAL FACTORS IN HPV-ASSOCIATED CANCERS

TOBACCO SMOKING & CERVICAL CANCER

- Cervical cancer is the third leading cancer among women worldwide.
- The causal role of persistent HPV infection in cervical cancer has been well established.
- It is worth studying the association between tobacco smoking and cervical cancer development.

STUDY HISTORY

1950's

- *Epidemiological evidence of the association between tobacco smoking and cervical cancer began to emerge.*

1977

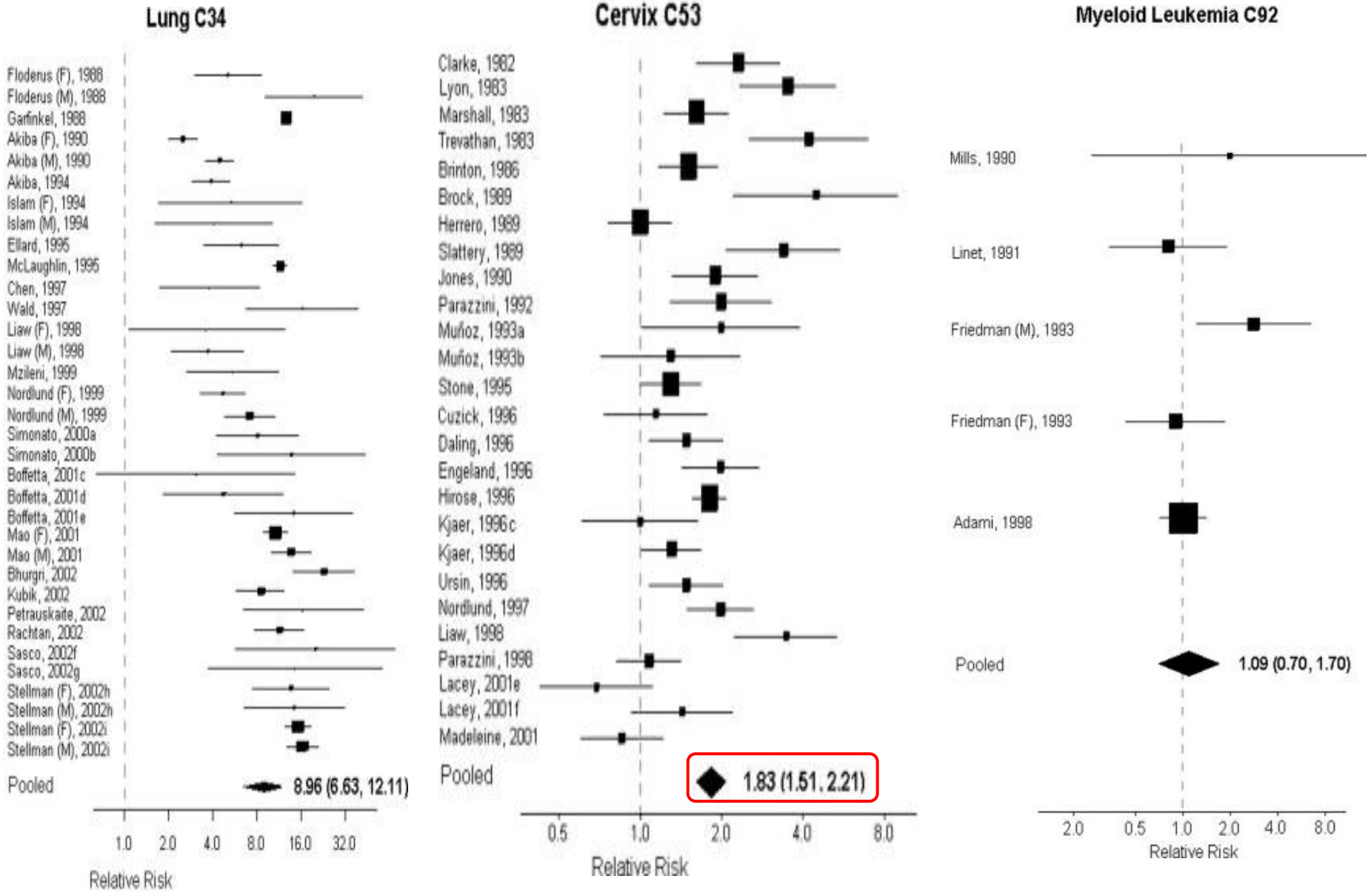
- *Winkelstein hypothesized that tobacco smoking was a causative factor for cervical cancer.*

- *"Ever-smokers have an excess risk of cervical cancer that persists after controlling for the strong effect of HPV and for other potential cofactors of progression from infection to cancer."*

2004

- *International Agency for Research on Cancer (IARC) added cervical cancer to the long list of smoking-related cancers.*

Forest plots for current smokers by cancer sites.



International Journal of Cancer. 2008 Jan 1;122(1):155-64.

2006

- "*Current* tobacco smoking is associated with an increased *risk of squamous cell carcinoma (SCC) but not for adenocarcinoma of the cervix.*"

2006

- "*Current smokers with a high HPV-16 viral load at time of first smear were at a particularly increased risk (27-fold) of cervical SCC compared with current smokers without HPV infection.*"

2008

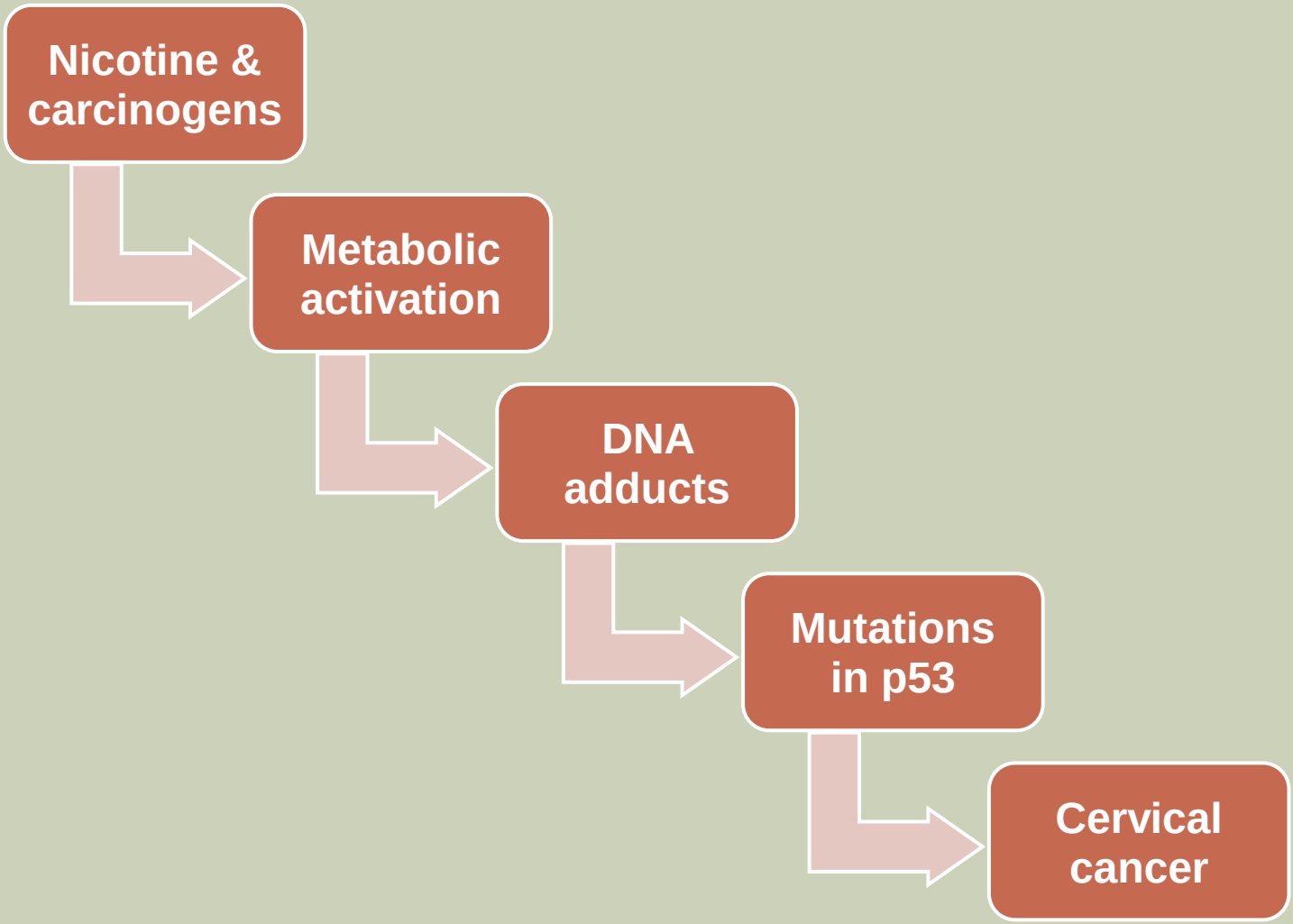
- "*The risk of being HPV-positive increased with increasing number of cigarettes smoked per day among current smokers, and women who reported to smoke 15 or more cigarettes daily had a 2-fold risk of HPV positivity as compared with never-smokers.*"

2009

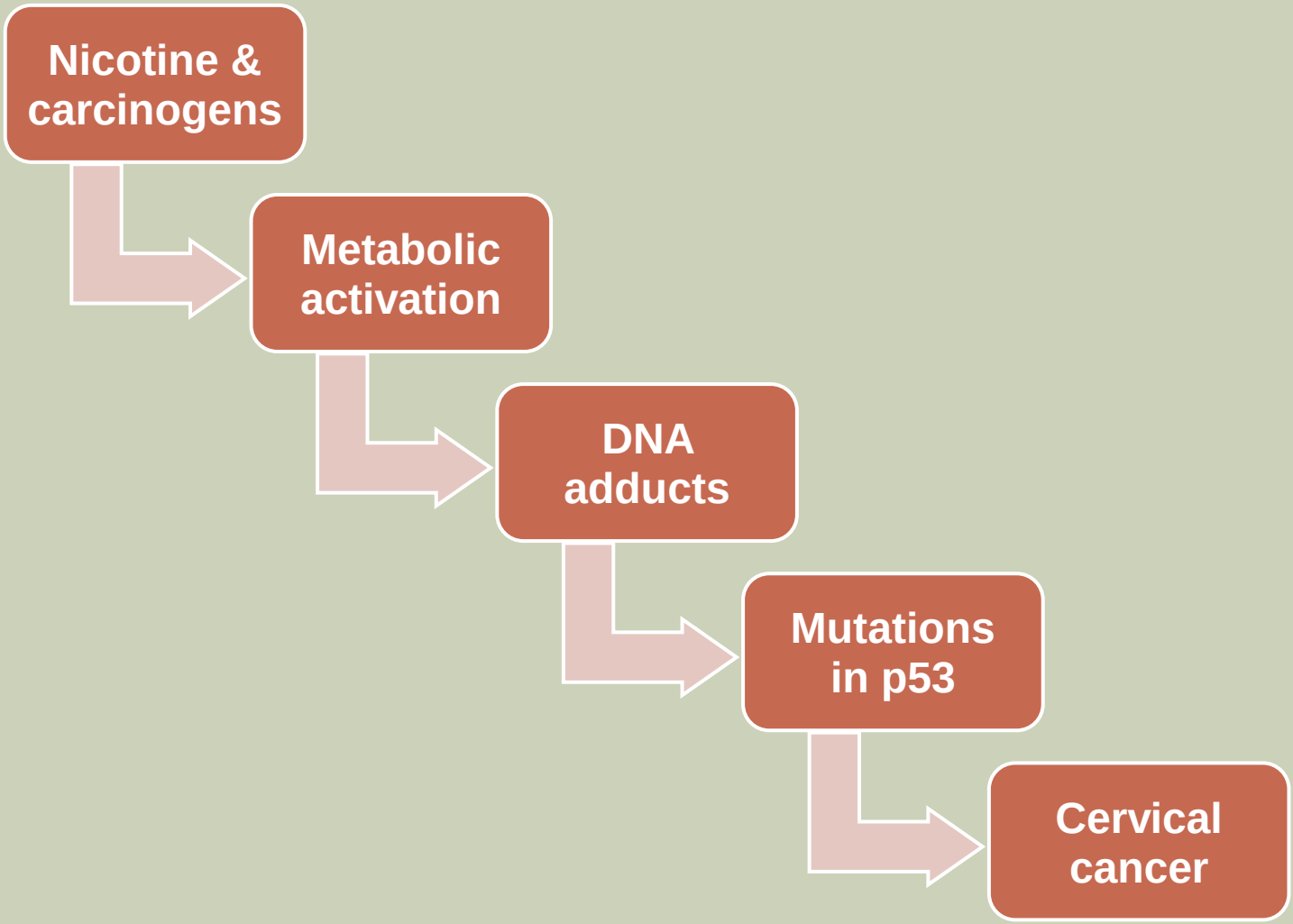
- "*Smoking* also affects survival among women diagnosed with *cervical cancer*. After adjustment for age and stage at diagnosis, *cell* type, rural residence, race, insurance coverage, and *treatment*-received, current smoker were 21% more likely to die *of cervical cancer* compared with known nonsmoking cases."

- *Unfortunately*, few smokers with cervical cancer quit or *decreased* consumption during treatment.

ONCOGENIC MECHANISMS



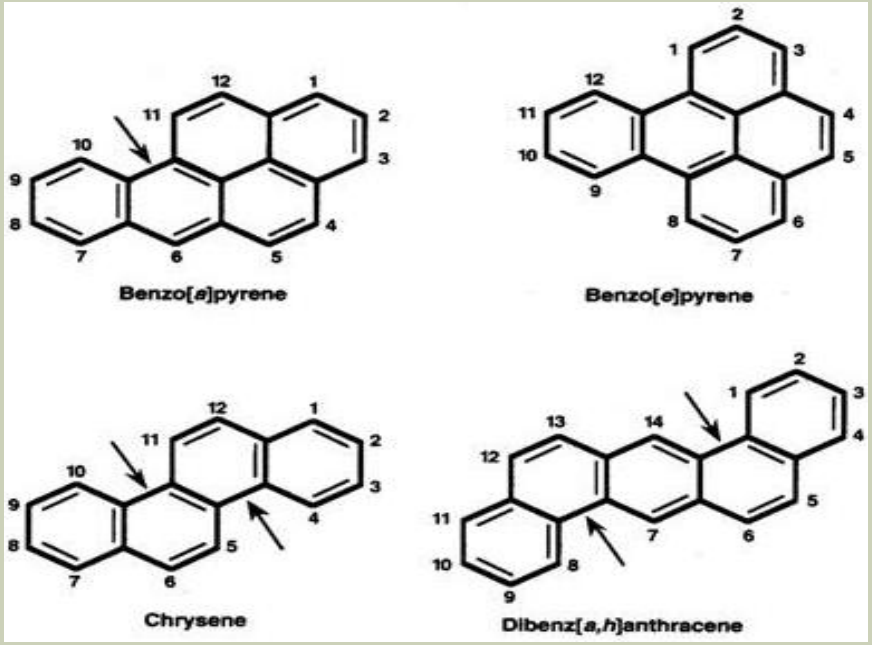
- Direct exposure of the DNA in cervical epithelial cells to nicotine and other carcinogens in tobacco smoke.
  - The in vivo effects of long-term nicotine exposure could affect persistent cellular proliferation, inhibition of apoptosis, and stimulation of vascular endothelial growth factor, with increased microvessel density.
  - In vitro studies in untransformed and transformed cell lines show that short-term exposure to nicotine or tobacco smoke extract is followed by changes in the expression of some DNA methyltransferases. Aberrant methylation of the *p16* tumor suppressor gene is strongly associated with current smoking in women with SCC and high-grade CIN.
  - Levels of nicotine were increased 40-fold and 4-fold, respectively, in the cervical mucus of healthy female smokers and in women with CIN as compared to serum levels.


Nicotine & carcinogens
Metabolic activation
DNA adducts
Mutations in p53
Cervical cancer

- Exposure to metabolic products of tobacco components, such as PAHs and aromatic amines, may cause the formation of DNA adducts and mutations in genes such as *p53* tumor suppressor gene.
- Additionally, exposure to tobacco may affect the ability of the host to mount an effective local immune response against viral infections.
  - The number of Langerhans cells and other markers of immune function substantially decreased in the cervix of smokers.

POLYCYCLIC AROMATIC HYDROCARBONS & CERVICAL CANCER

- "Polycyclic Aromatic Hydrocarbons (PAHs)" refer to a ubiquitous group of potent environmental pollutants that consist of fused aromatic rings.
- PAH mixtures have been classified as carcinogens to humans by IARC.
- Benzo[a]pyrene (BaP), the first chemically identified carcinogen, is the most extensively studied PAH.



CHEMICAL CHARACTERISTICS

- High melting and boiling points, low vapor pressure, and very low aqueous solubility;
- Highly lipophilic and therefore very soluble in organic solvents;
- Light sensitivity, heat resistance, conductivity, emittability, corrosion resistance, and physiological action.

SOURCE

- PAHs originate mainly from incomplete combustion of organic material such as coal, wood, gasoline, garbage and tobacco.

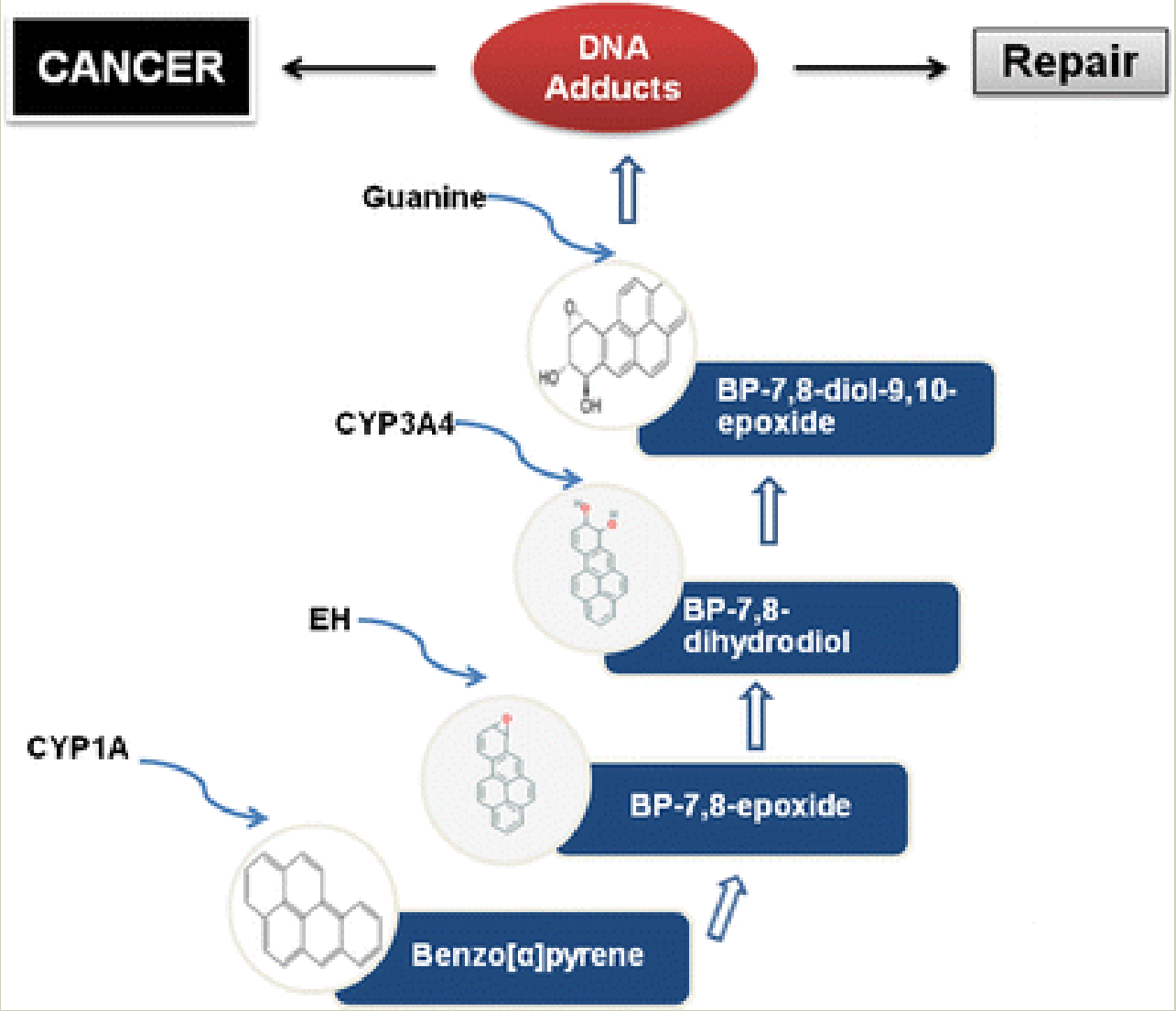
ROUTES OF EXPOSURE

- Ingestion, inhalation, and dermal contact in both occupational and non-occupational settings.
  - Dietary exposure includes smoked and grilled foods and foods that are contaminated by ambient air pollution.
  - Tobacco smoking contains a variety of PAHs, such as BaP;
  - Occupational exposure may occur in workers breathing exhaust fumes, as well as those involved in mining, metal working, or oil refining.

ONCOGENIC MECHANISMS

- PAHs may upregulate amplification of HPV genome and increase the probability of viral DNA integration into the host genome - a milestone in the development of cervical cancer.
- The reactive metabolites, such as epoxides and dihydrodiols, of PAHs can bind to cellular proteins and DNA. The resulting biochemical disruptions and cell damage lead to mutations, developmental malformations, and cancer.

Metabolic activation of BaP by the CYP enzyme system causing the formation of DNA adduct and leading to cancer.



Tumor Biology. 2012 Oct;33(5):1265-74. doi: 10.1007/s13277-012-0413-4.

ULTRAVIOLET EXPOSURE, HPV & NON-MELANOMA SKIN CANCER

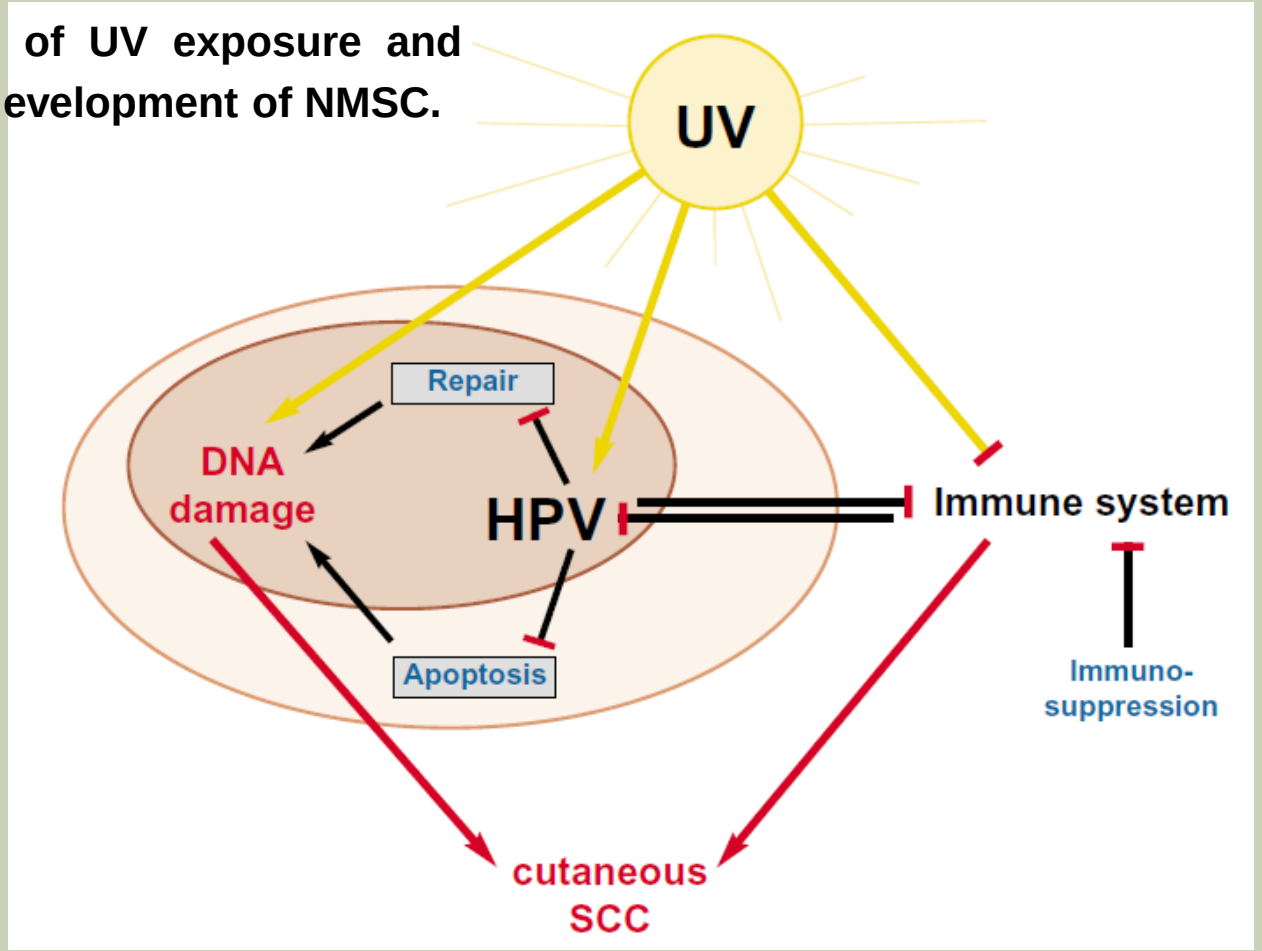
- Non-melanoma skin cancer (NMSC) is the most common cancer among Caucasians.
- Ultraviolet (UV) exposure has been recognized as a major risk factor in the development of NMSC.
- Recent research has focused on the association between HPV infection and skin cancer, especially cutaneous SCC.

HPV IN NMSC

- Increasing clinical and epidemiological data support a role of cutaneous HPV in NMSC development.
  - HPV DNA was detected in 90% of premalignant skin lesions and SCCs from epidermodysplasia verruciformis (EV) patients;
  - The prevalence of cutaneous HPV DNA was near 100% in premalignant skin lesions and SCCs in immunocompromised individuals, and was 30-60% in SCCs from immunocompetent patients;
  - Anti-HPV antibodies were found 60% more often in cases of SCC compared to controls. Beta-HPVs were associated with SCC even after adjusting for smoking, drinking, medical and family history, and sun exposure.

ONCOGENIC MECHANISMS

Synergistic interaction of UV exposure and cutaneous HPV in the development of NMSC.



Disease Markers. 2007;23(4):247-59.

SUMMARY

- Environmental factors play an important role in the development of virus-associated human cancers.
- Several mechanisms have been suggested through how tobacco smoking contributes to cervical carcinogenesis.
  - Direct exposure of the DNA in cervical epithelial cells to nicotine and other carcinogens in tobacco smoke can lead to cervical cancer via a variety of processes;
  - Exposure to metabolic products of tobacco components, such as PAHs and aromatic amines, may cause the formation of DNA adducts and mutations in genes such as *p53*.
  - Additionally, exposure to tobacco may affect the ability of the host to mount an effective local immune response against viral infections.

- PAHs are a class of carcinogenic environmental pollutants that generated from incomplete combustion of organic material.
- Long-term exposure to PAHs may cause DNA adduct and decreased immune function of the host, as well as upregulation of HPV genome amplification which increases probability of viral DNA integration into the host genome, thereby results in cervical cancer development.
- UV exposure can interact with cutaneous HPV to inhibit the DNA repair mechanisms and apoptotic activities of the host cell, leading to the early onset of skin carcinogenesis.

THANK YOU!

The End.