

Skin Cancer/Sunscreen -- the Dilemma

UCSD Department of Family
and Preventive Medicine



Vitamin D Workshop

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DISCLOSURES

The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

No relationships to disclose.

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Objectives

Describe the epidemiology of cutaneous malignant melanoma in terms of:

Person, Place, and Time

Identify risk factors for melanoma

Individual and behavioral characteristics

Environmental risk factors

Differentiate between two kinds of ultraviolet irradiance:

UVA and UVB

Understand the difference between primary and secondary prevention of melanoma

Make recommendations for primary prevention of melanoma based on its epidemiology



Screening: Secondary Prevention



ABCD screening guidelines:

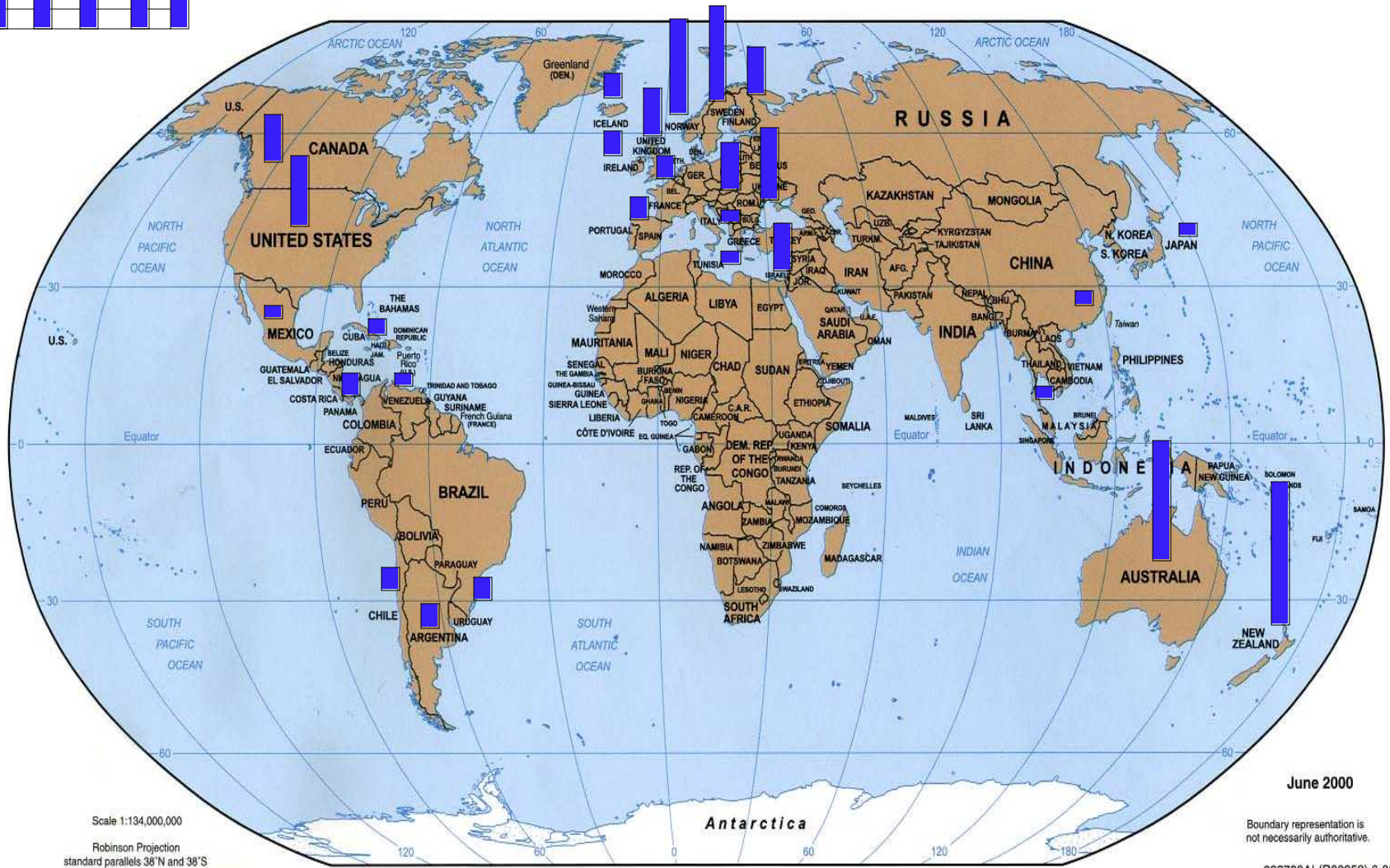
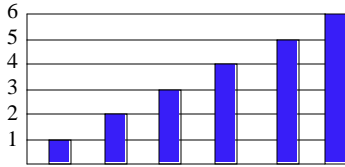
Asymmetry - uneven in shape or color

Border - is irregular

Color - flag sign is a mole that has red, white,
and blue colors

Diameter-increases or is greater than 6 millimeters

Melanoma: Person and Place

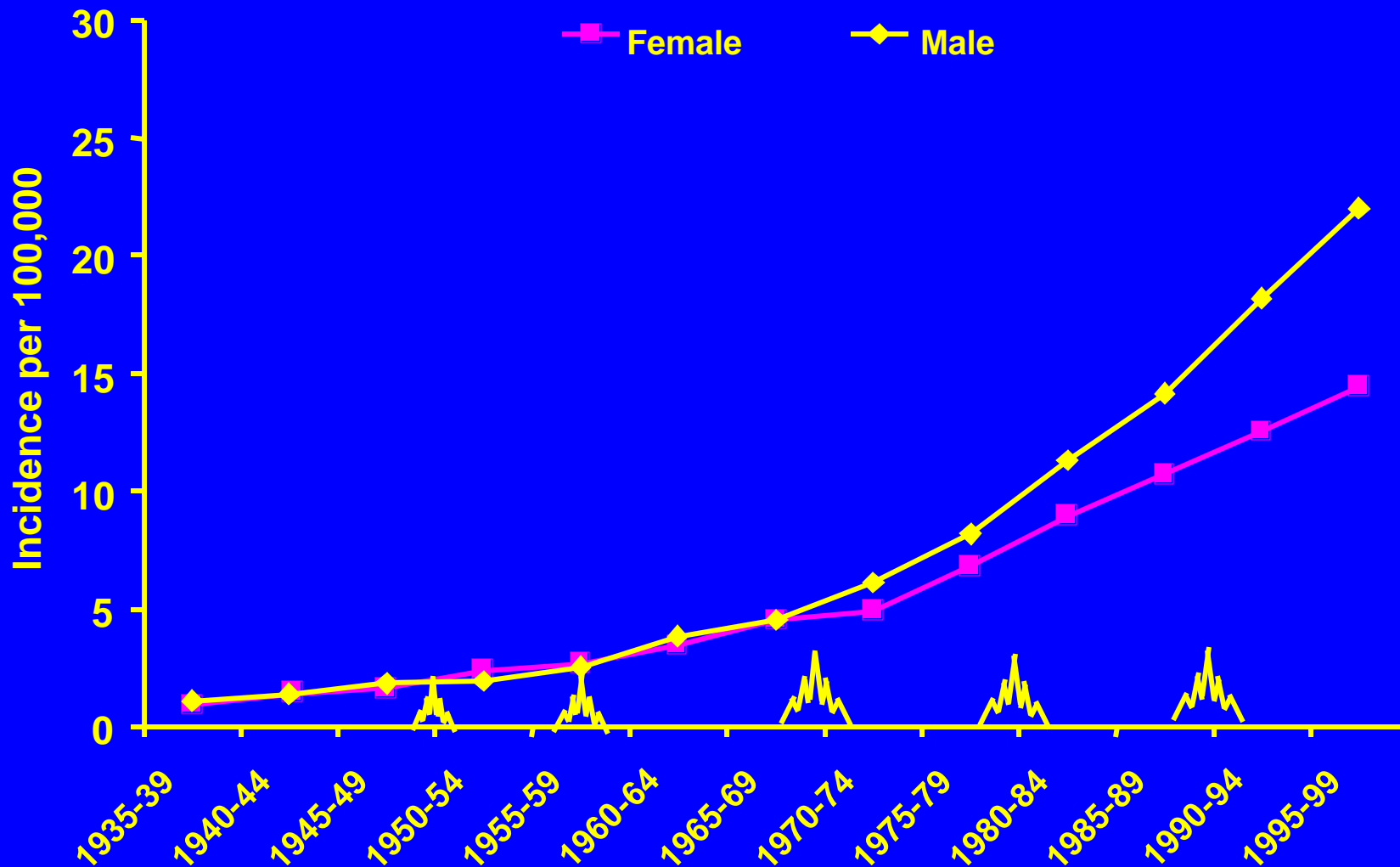


Age-adjusted melanoma mortality rates in men, 2002
Global burden 160,000 cases, 41,000 deaths, both sexes

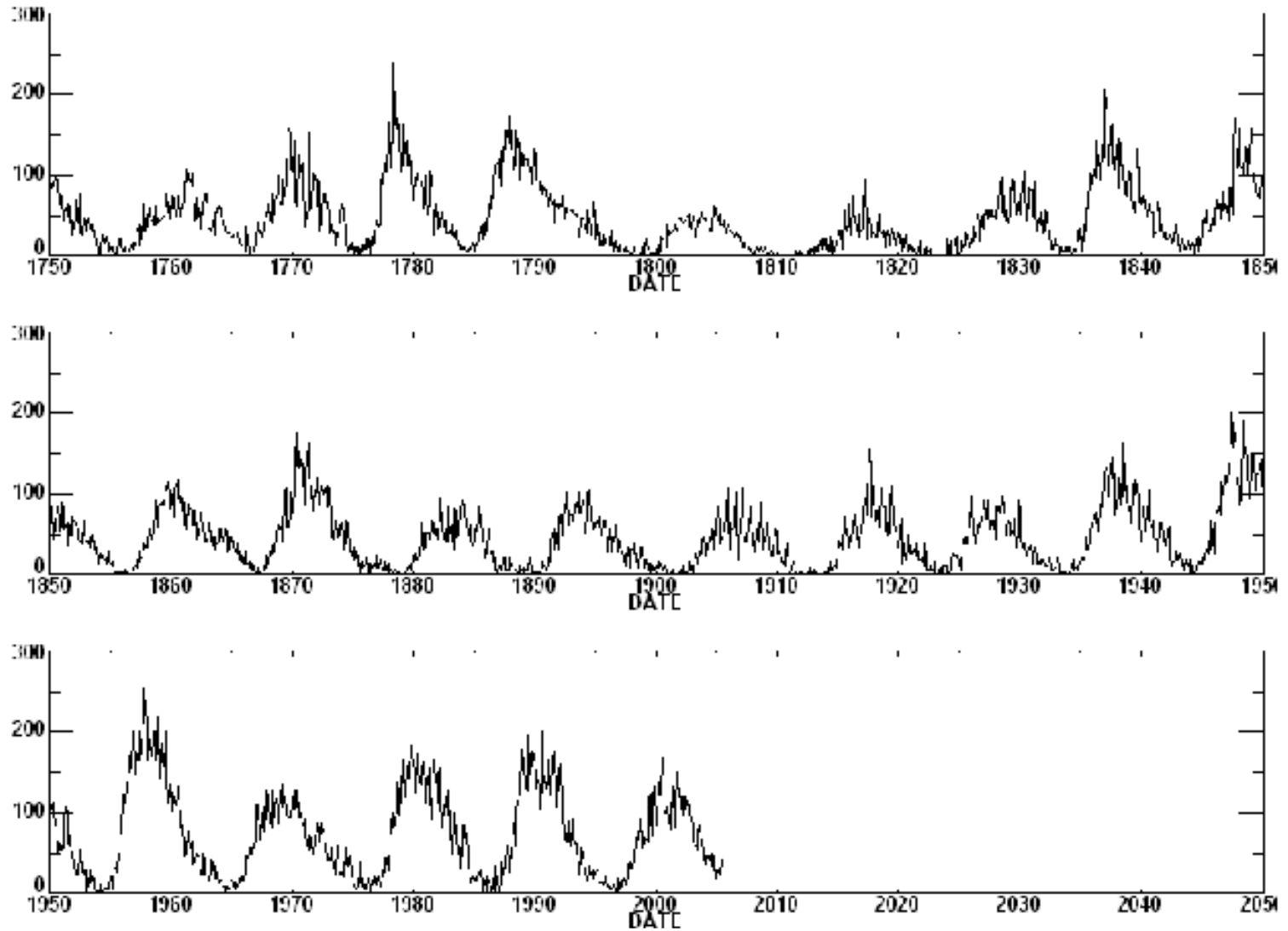
Melanoma: Place and Time

Melanoma incidence in Connecticut, 1935-1999

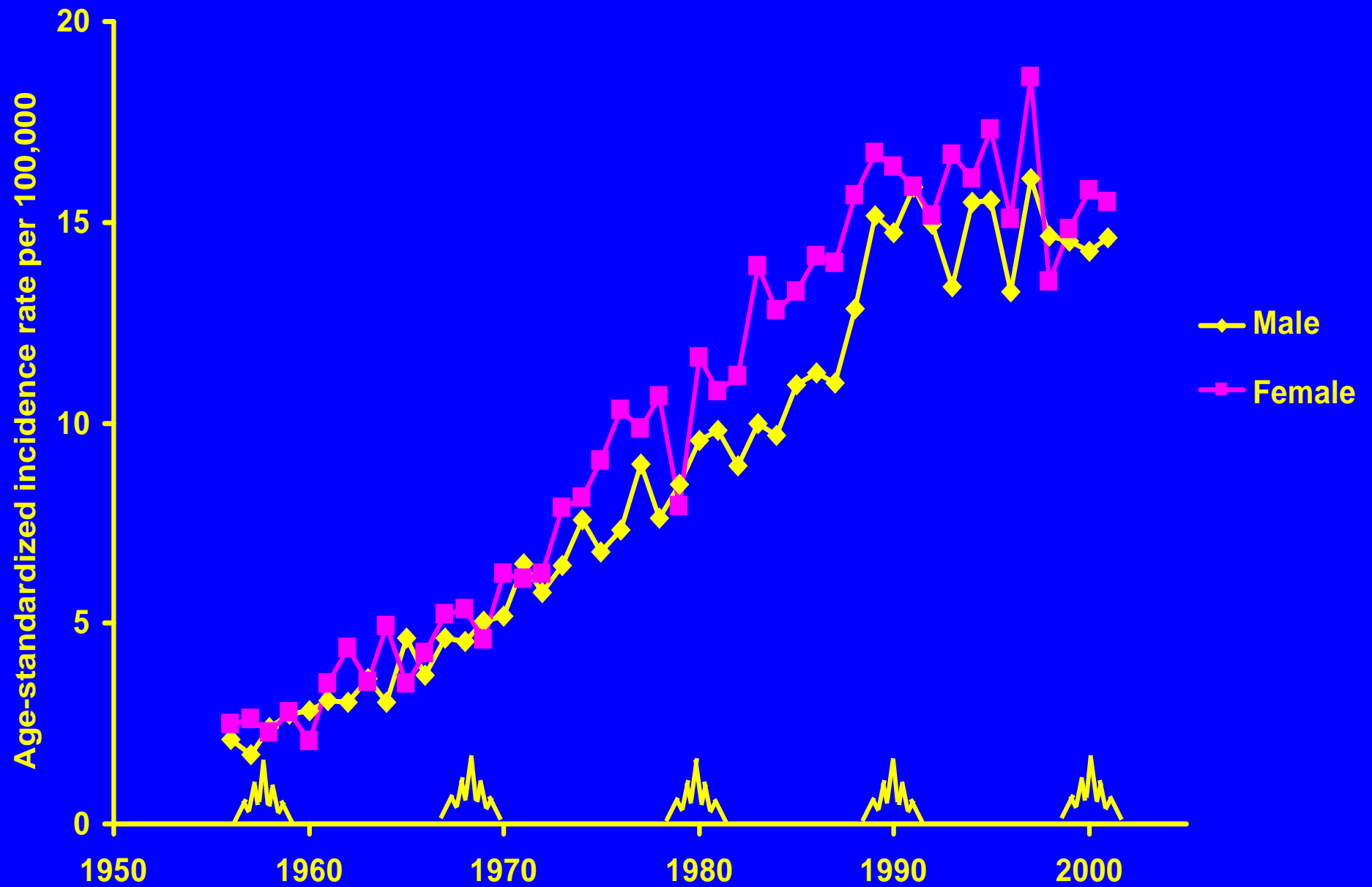
Source: Connecticut Tumor Registry



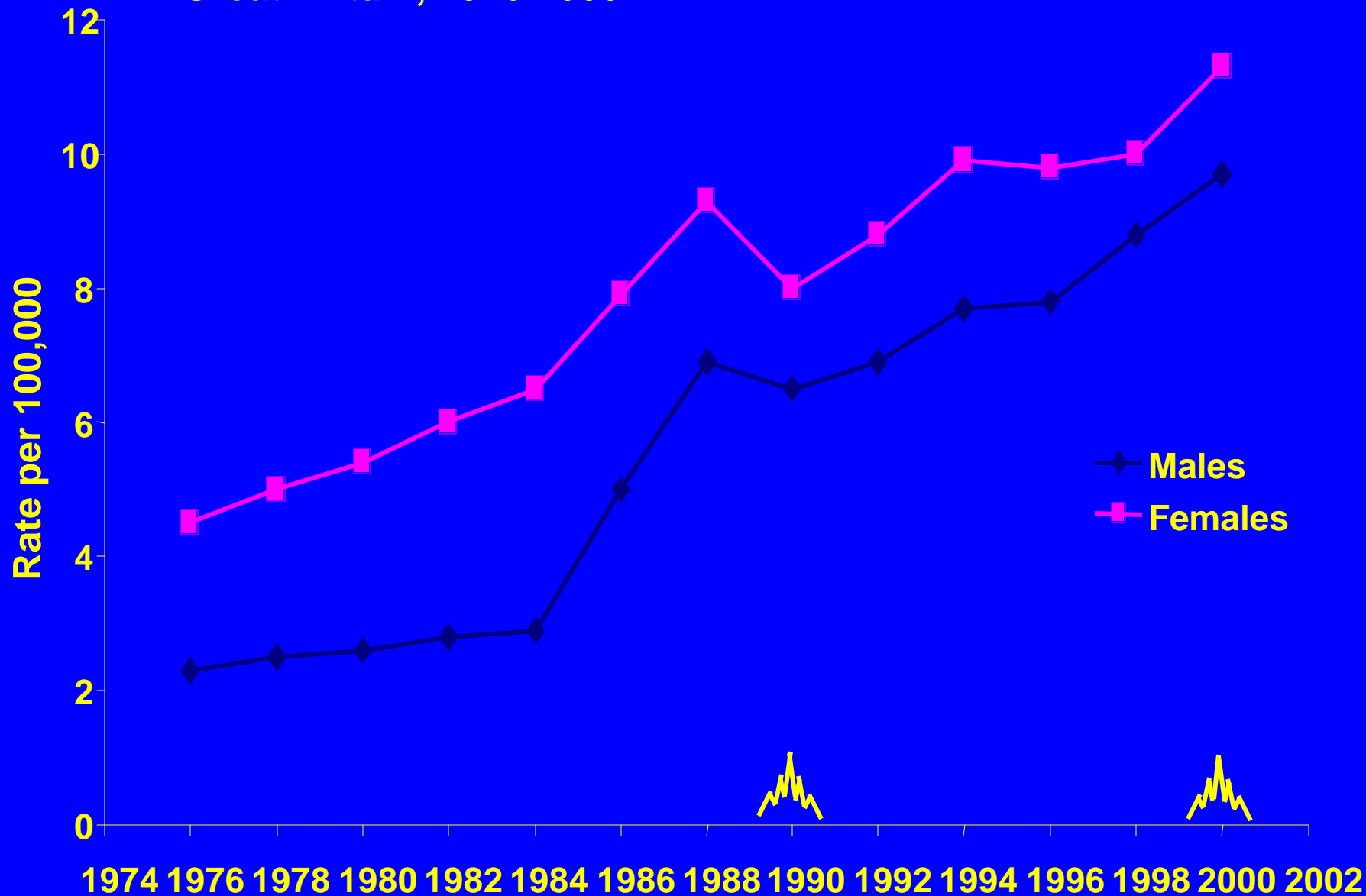
Monthly Average Sunspot Number, 1750-2005



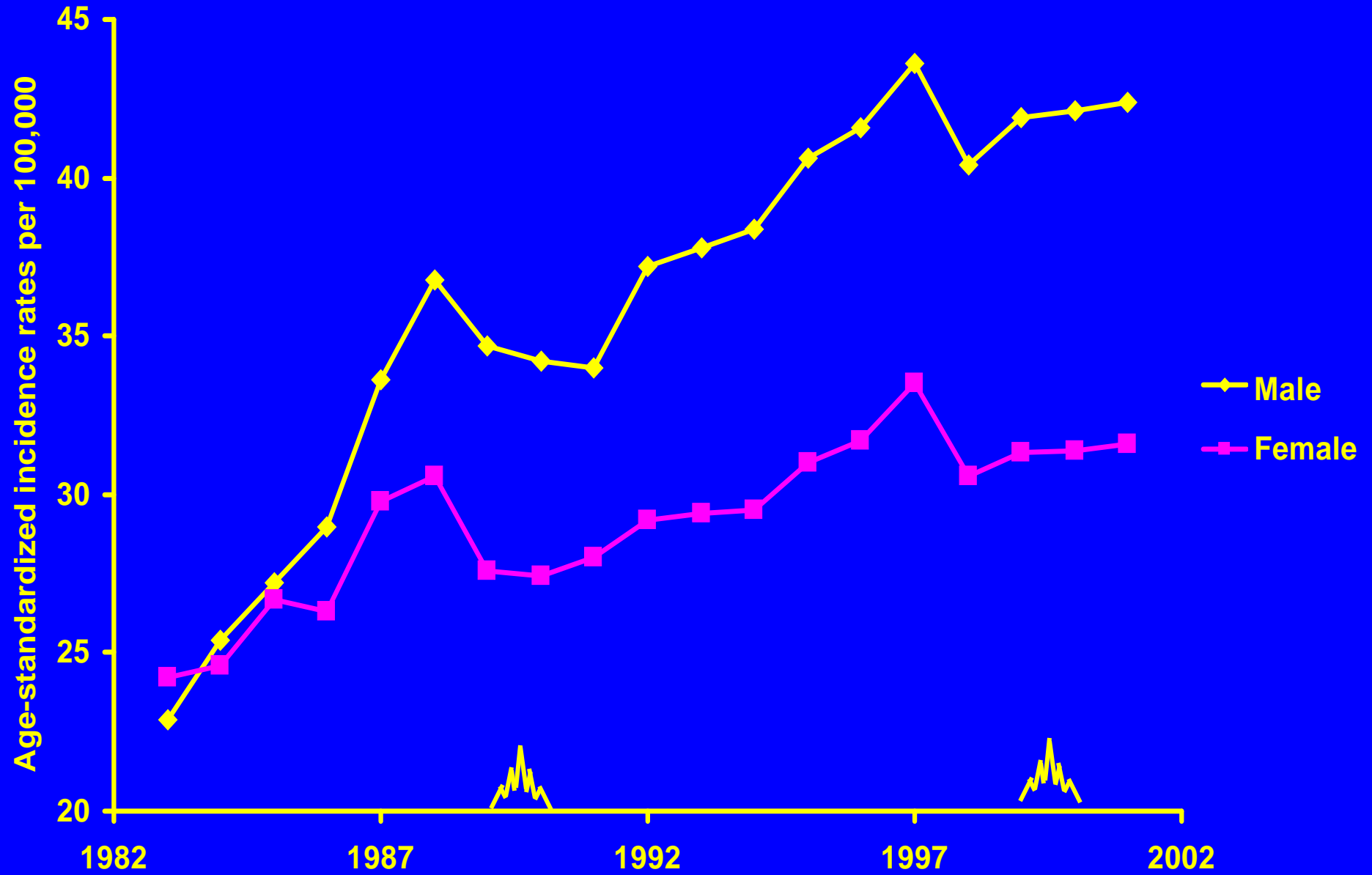
Melanoma incidence in Norway, 1956-2001
Source: Cancer Registry of Norway



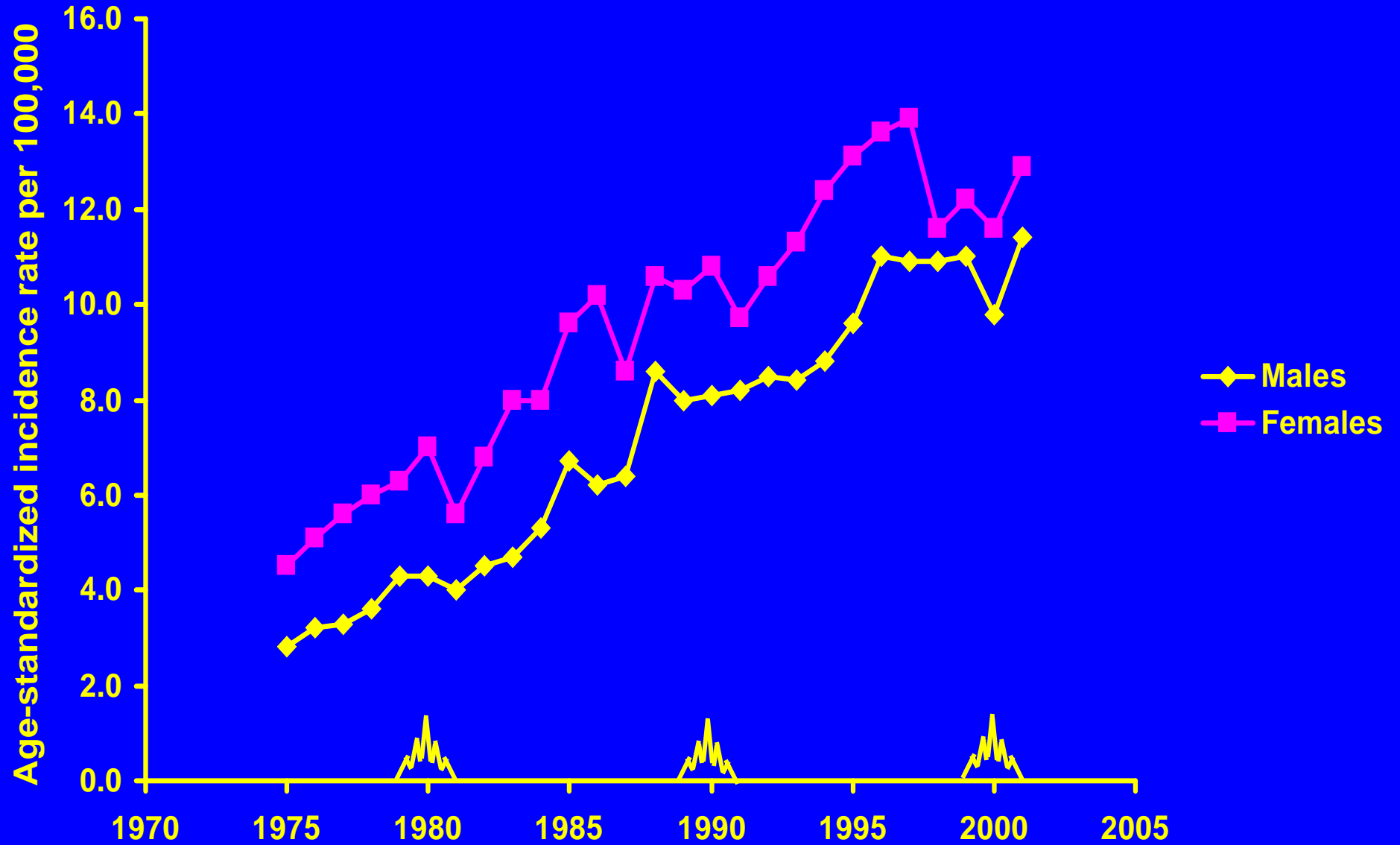
Age-standardised incidence rates by sex, malignant melanoma, Great Britain, 1976-2000



Melanoma incidence in Australia, 1983 - 2002
Source: Australian Institute of Health and Welfare



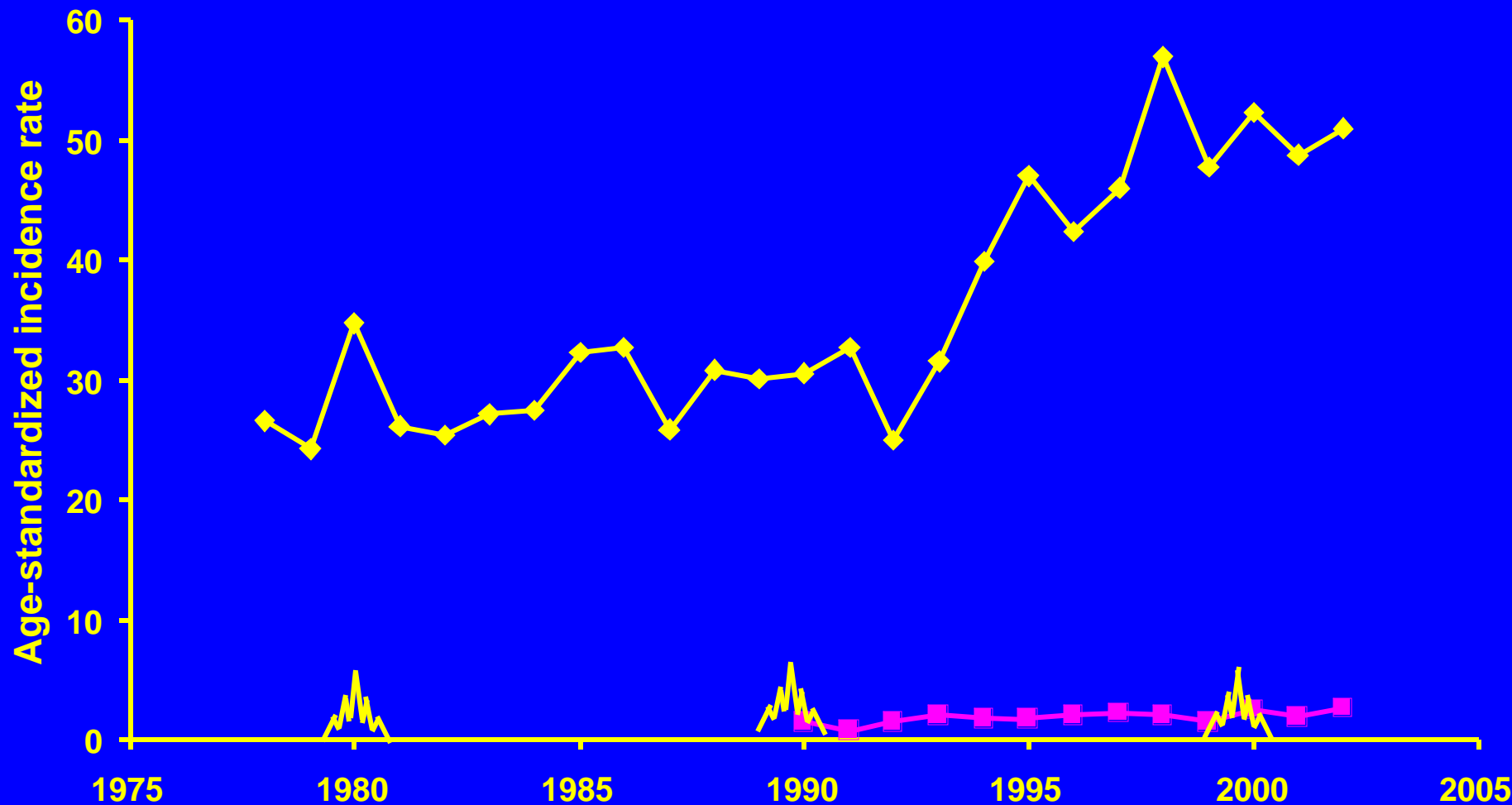
Melanoma incidence in Scotland, 1975-2001
Source: National Health Service of Scotland

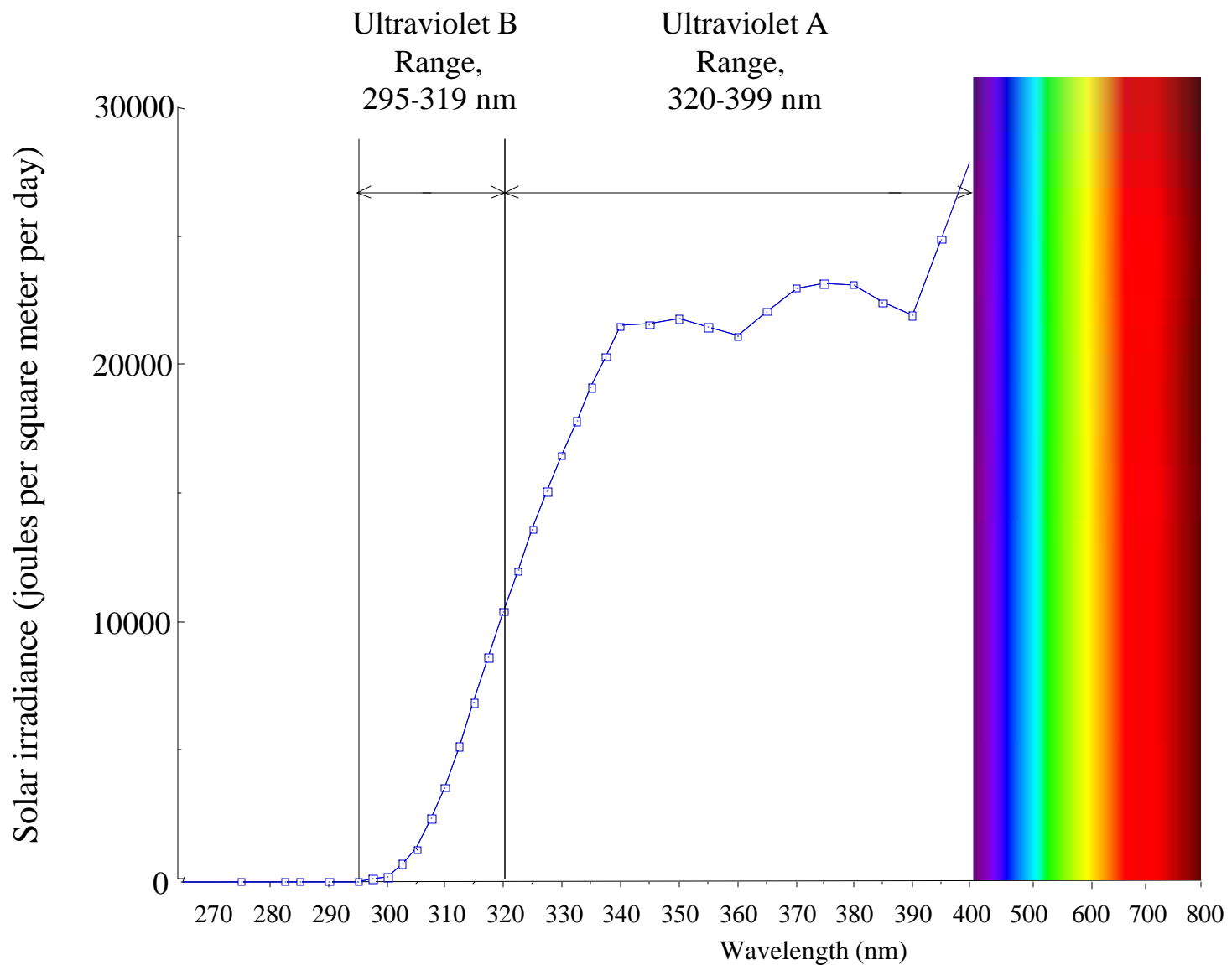


Melanoma incidence in Hawaii, 1977-2002

Source: Hawaii Tumor Registry

◆ Whites ■ Asian Pacific Islander

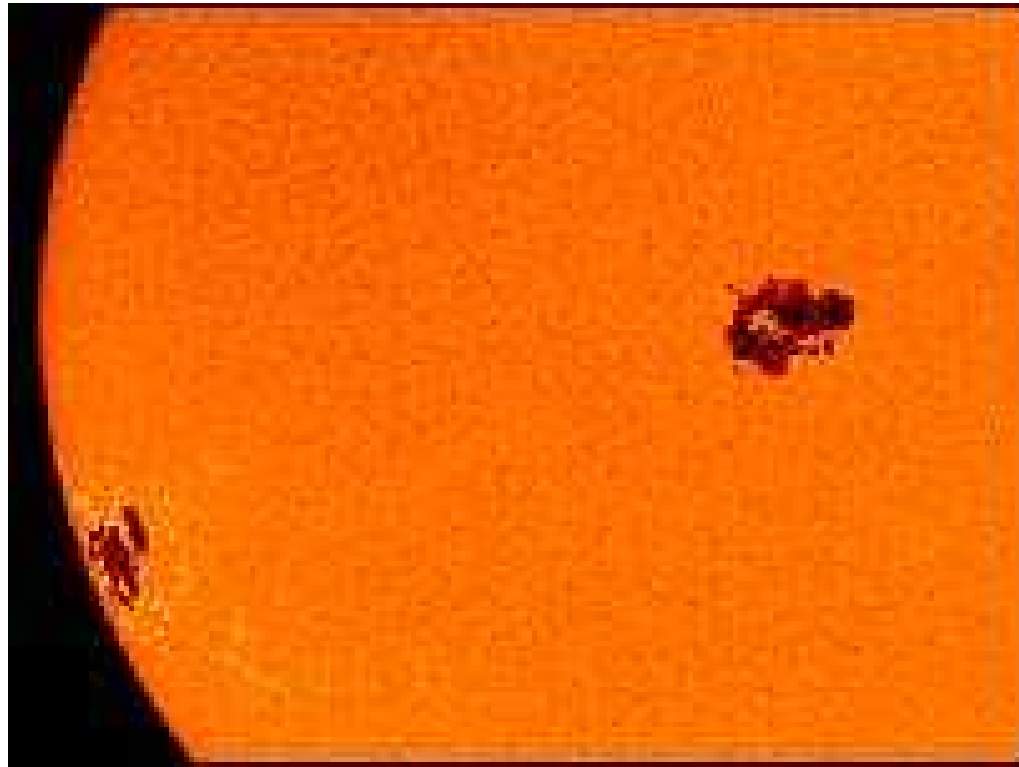




Solar ultraviolet irradiance

Visible light

Role of UVB in Vitamin D Synthesis



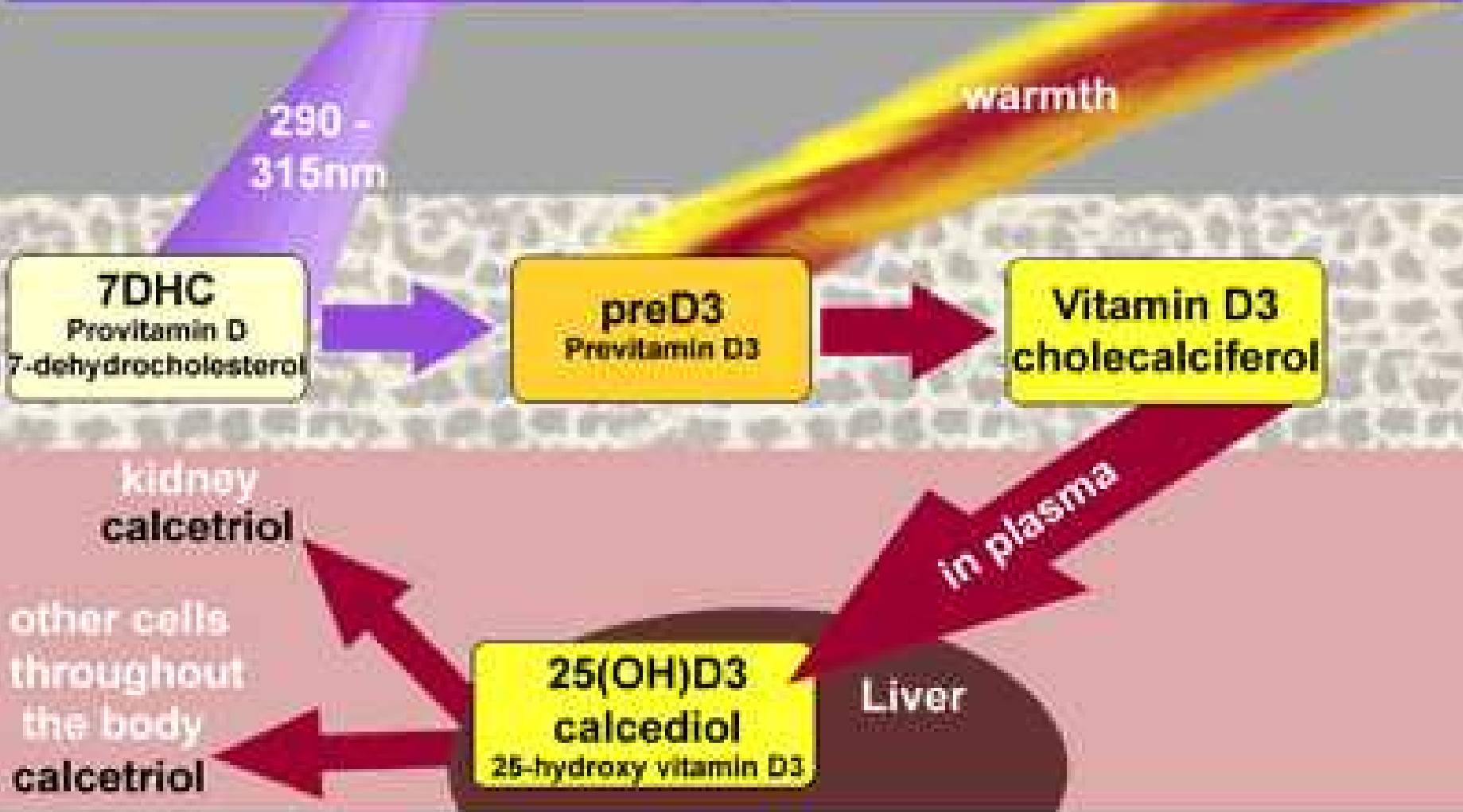
The sun is the source of UVB used to make vitamin D. (Photo: Stanford Univ.).

Less than 1% of solar radiation is UVB.

Four UVB photons combine with one molecule of cholesterol (7DHC)

Opens a ring to make previtamin D

Warmth converts to vitamin D in skin (chlocalciferol)



Laboratory Studies

In vitro studies find that vitamin D is a potent antiproliferative agent against various tumor cells including malignant melanoma ¹

25 (OH) vitamin D (calcidiol) or 1,25 (OH)₂ vitamin D (calcitriol) inhibited growth in a human melanoma cell line (ME18) to approximately 60 percent ²

Studies have found a dose- and time- dependence of this anti-proliferative effect ²

1) Pelczynska M, Switalska M, Maciejewska M, Jaroszewicz I, Kutner A, Opolski A. Antiproliferative activity of vitamin D compounds in combination with cytostatics. *Anticancer Research* 2006;26:2701-5

2) Gruber BM, Anuszevska EL. Influence of vitamin D3 metabolites on cell proliferation and cytotoxicity of adriamycin in human normal and neoplastic cells. *Toxicol In Vitro*. 2002;16:663-7.

Sun exposure is associated with increased survival from melanoma

Solar elastosis (present versus absent) was associated with a 60% increase in survival in patients with malignant melanoma (HR = 0.4, 95% CI = 0.2 to 0.8, P = 0.009)

Sunburn and history of high intermittent sun exposure were also statistically significantly inversely associated with death from melanoma

Source: Berwick M, Armstrong BK, Ben-Porat L, Fine J, Kricger A, Eberle C, Barnhill R. Sun exposure and mortality from melanoma. *J Natl Cancer Inst.* 2005;97:195-9.

Vitamin D and melanoma

| Vitamin D Quintile | Vitamin D Intake | Melanoma cases | Controls | Total |
|--------------------|------------------|----------------|----------|-------|
| Highest | > 158 IU | 84 | 112 | 196 |
| Lowest | < 58 IU | 120 | 112 | 232 |
| Total | | 204 | 224 | 428 |

Odds ratio = 0.67 p -value < 0.05 p -value for trend = 0.03

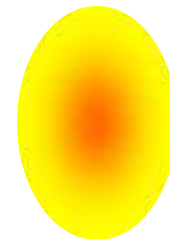
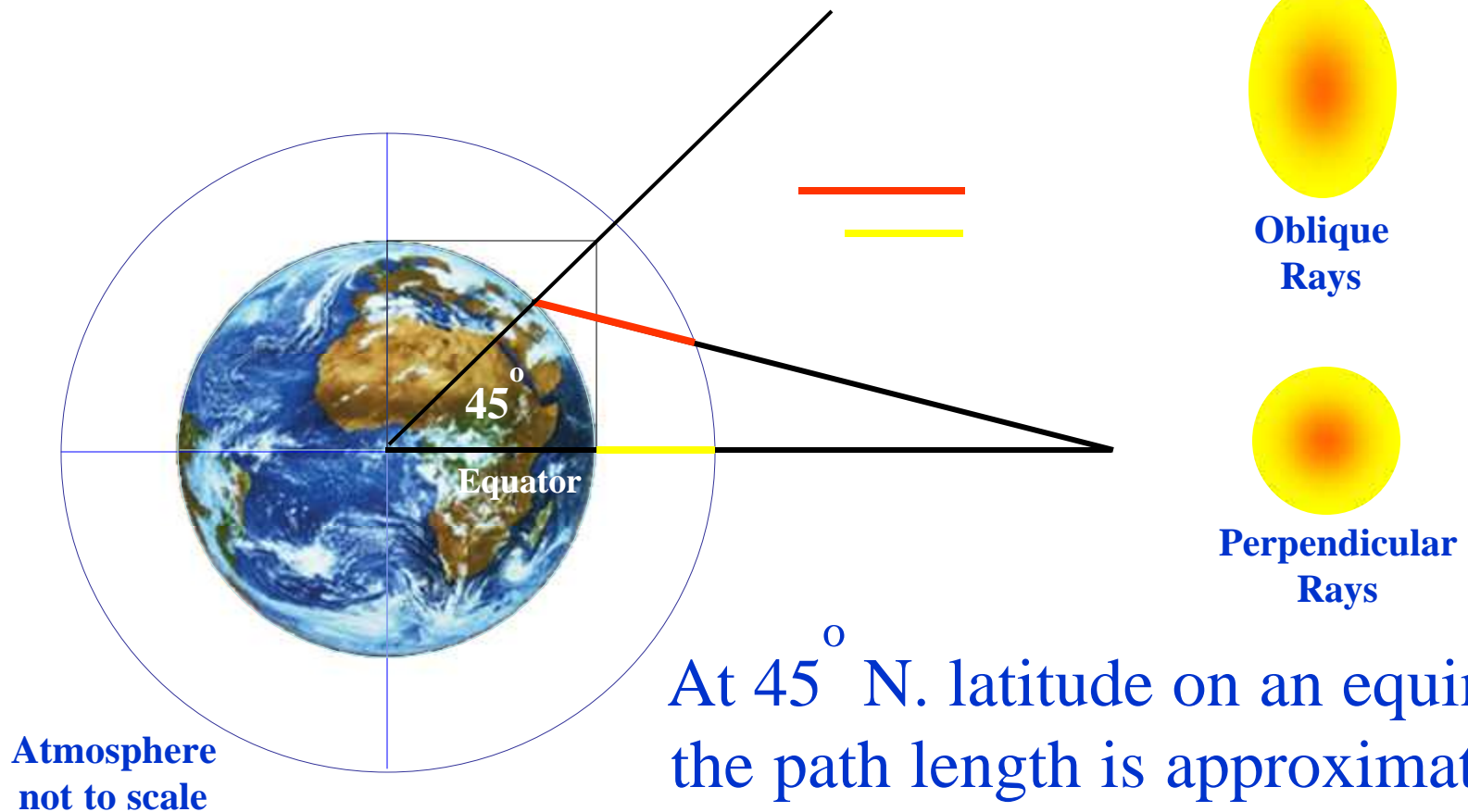
Adjusted* Odds ratio = 0.61 (95% CI = 0.40-0.95) p -value < 0.05

* Adjusted for age, race, sex, study site, number of nevi, and skin response.

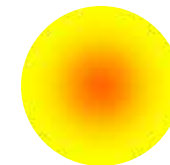
†Source: Millen AE, Tucker MA, Hartge P, et al. Diet and melanoma in a case-control study. Cancer Epidemiol Biomark Prev 2004;13:1042-51.

UVB varies by Solar Angle which changes with Season, Latitude, and Time of Day

The flashlight beam model



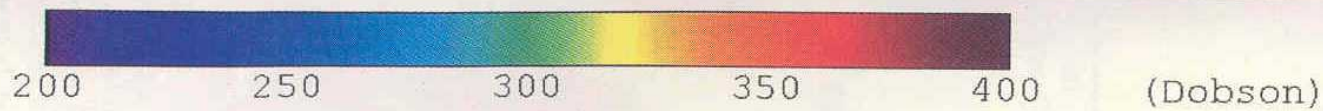
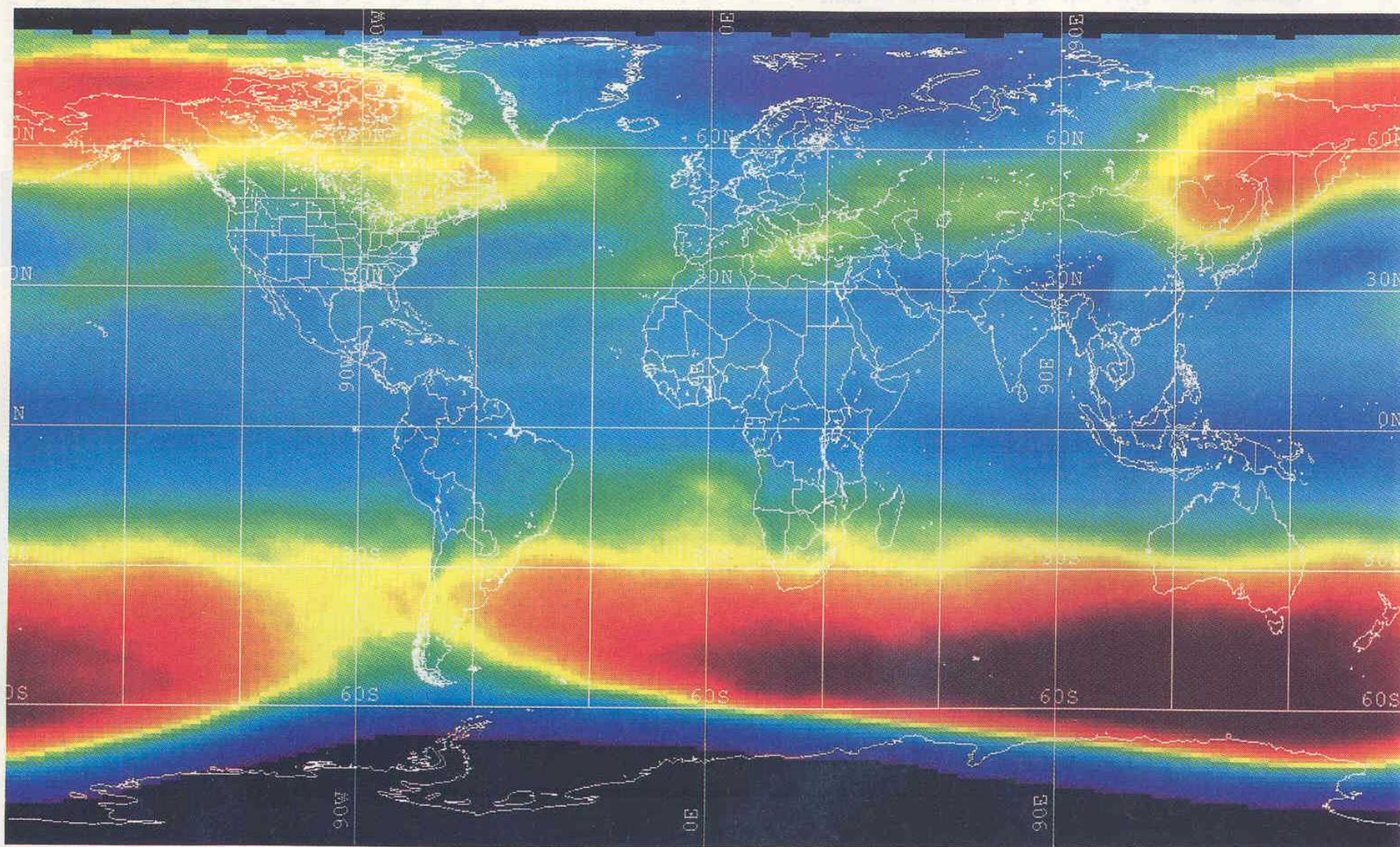
Oblique Rays



Perpendicular Rays

At 45° N. latitude on an equinox the path length is approximately 40% longer than at the equator

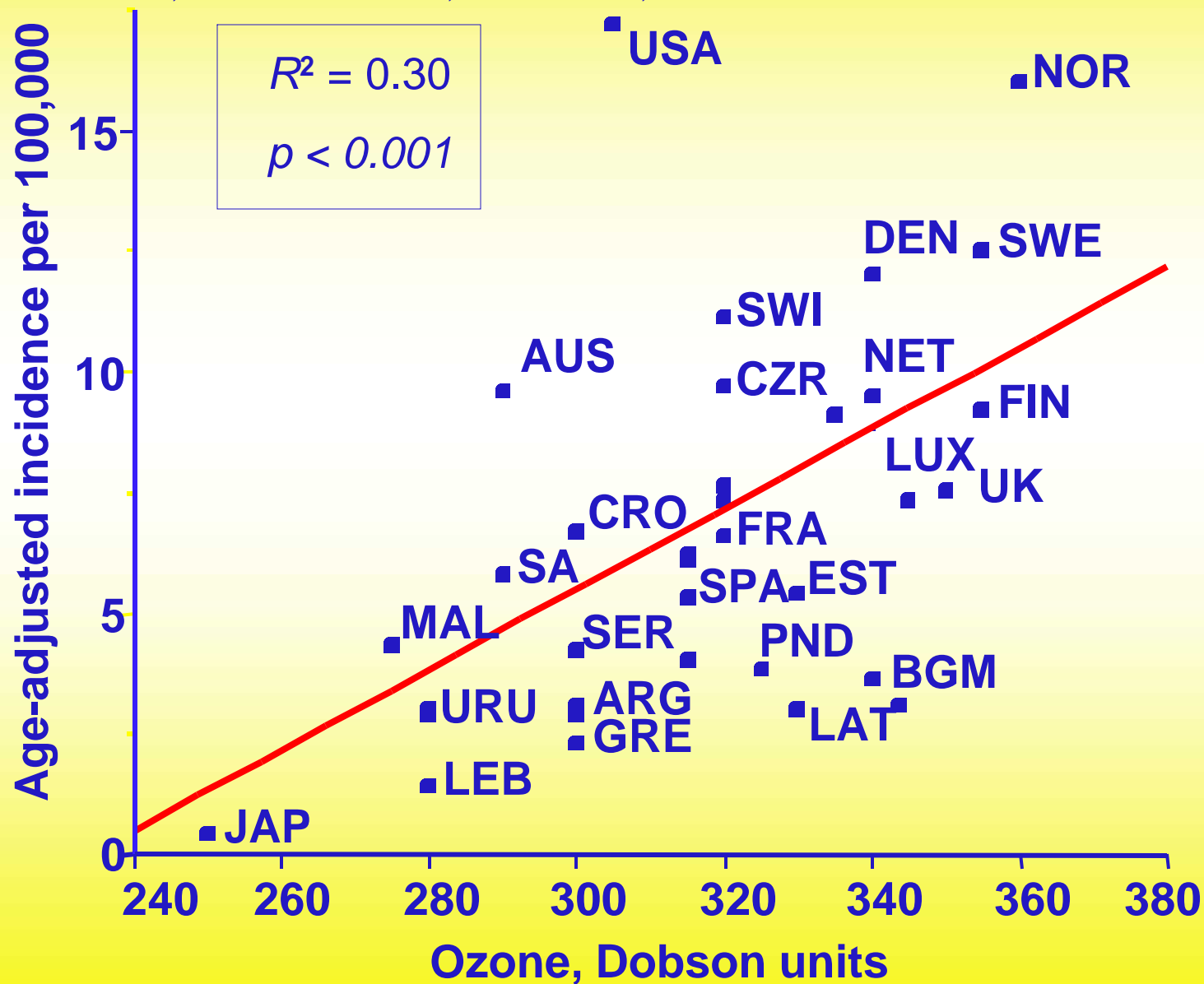
B. OCTOBER 1989



Total Column Ozone (Dobson units)

Age-adjusted melanoma incidence rates per 100,000 by stratospheric ozone thickness, 36 industrialized countries

Sources: Ozone, NASA TOMS; Incidence, IARC 2002



Ozone, pigmentation, and melanoma

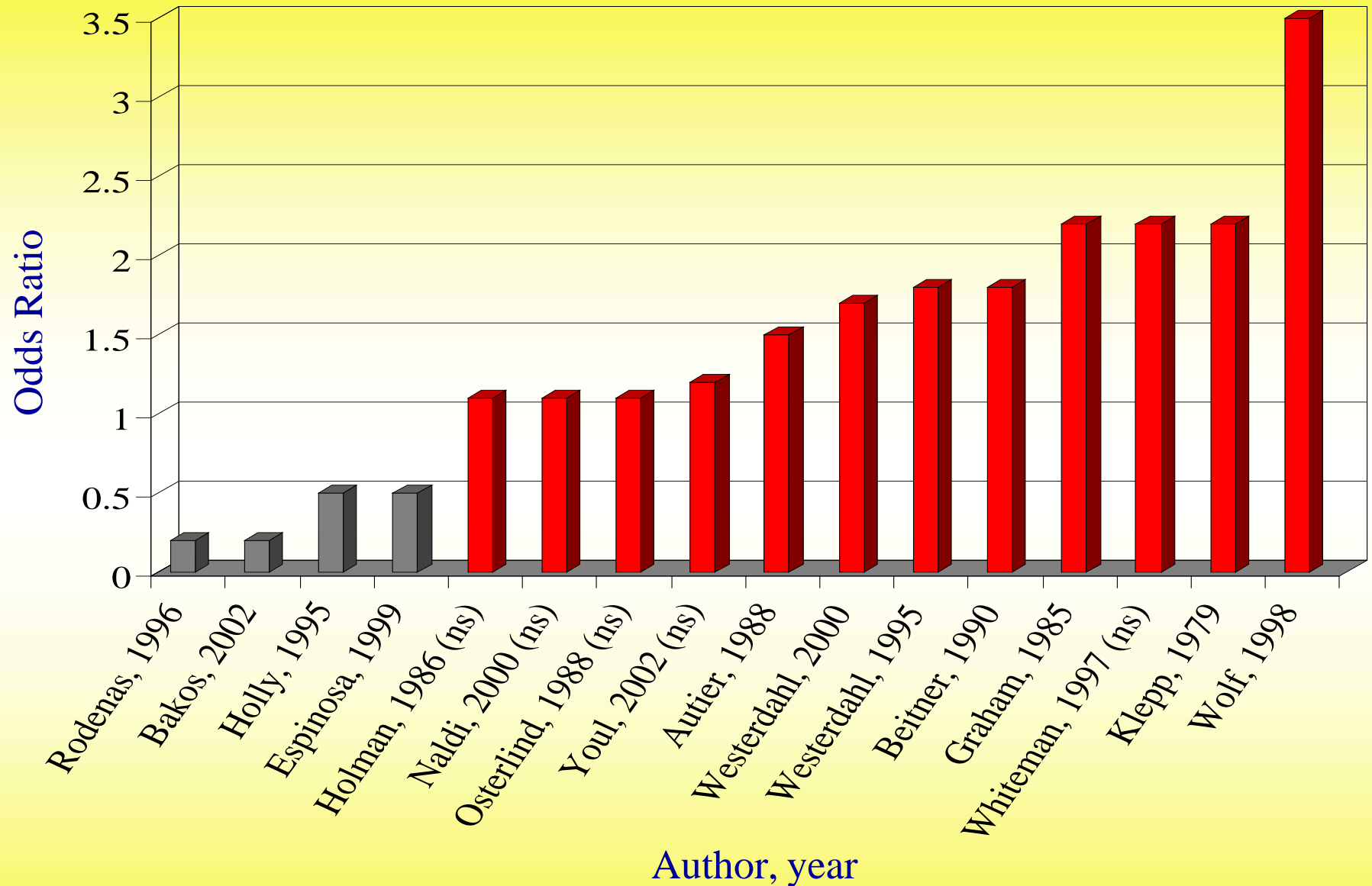
| Variable | Regression coefficient | Standard error | <i>t</i> | <i>p</i> |
|---------------------------|------------------------|----------------|----------|----------|
| Ozone* | 0.0346 | 0.0064 | 5.34 | < 0.0001 |
| Pigmentation [†] | -0.9838 | 0.2622 | -3.75 | 0.0002 |

$$R^2 = 0.43, p < 0.0001$$

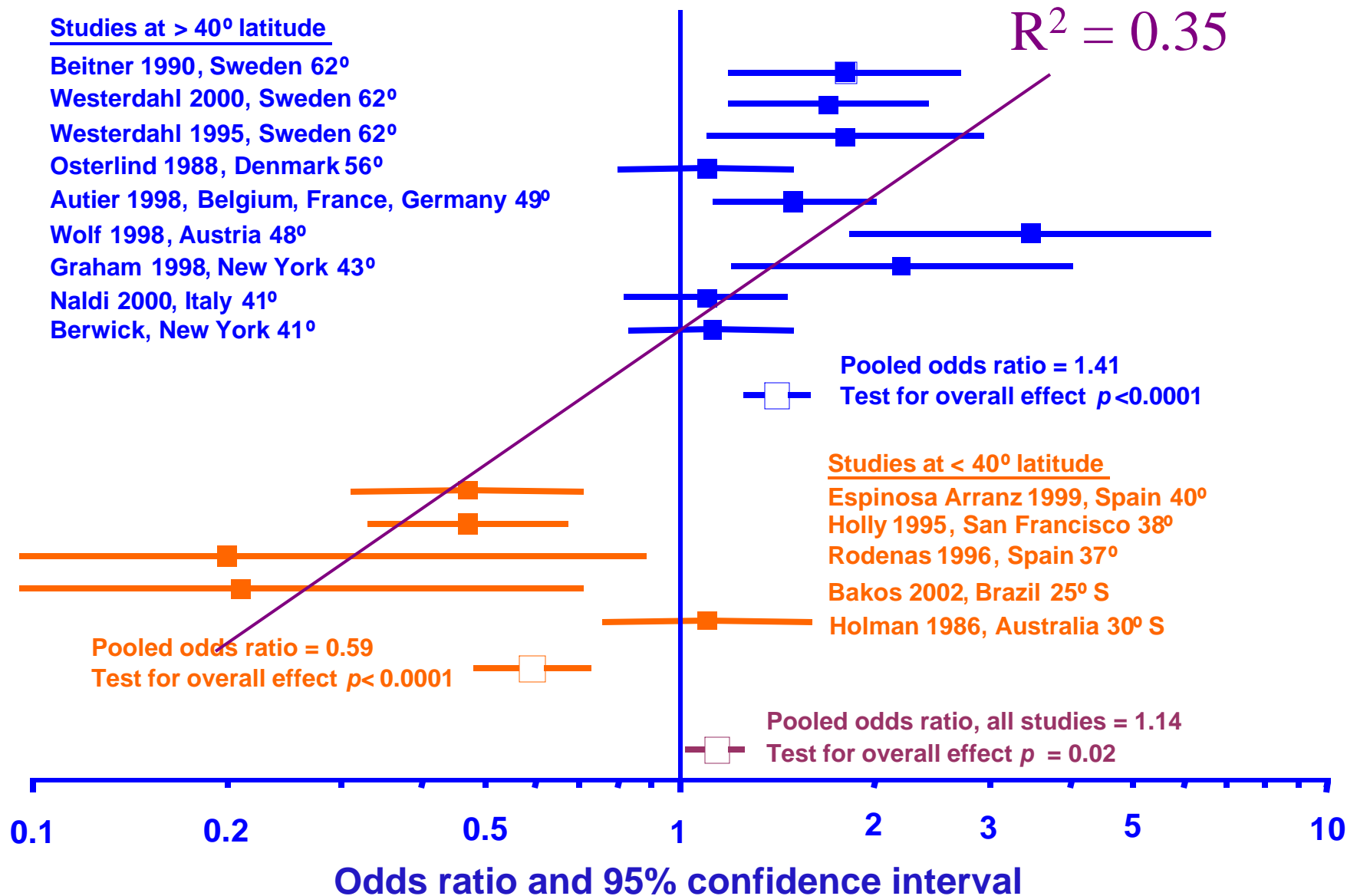
*Ozone in Dobson units. Source: NASA TOMS Satellite package

†Source: Jablonski and Chaplin, J Hum Evol 2000; 39:57-106.

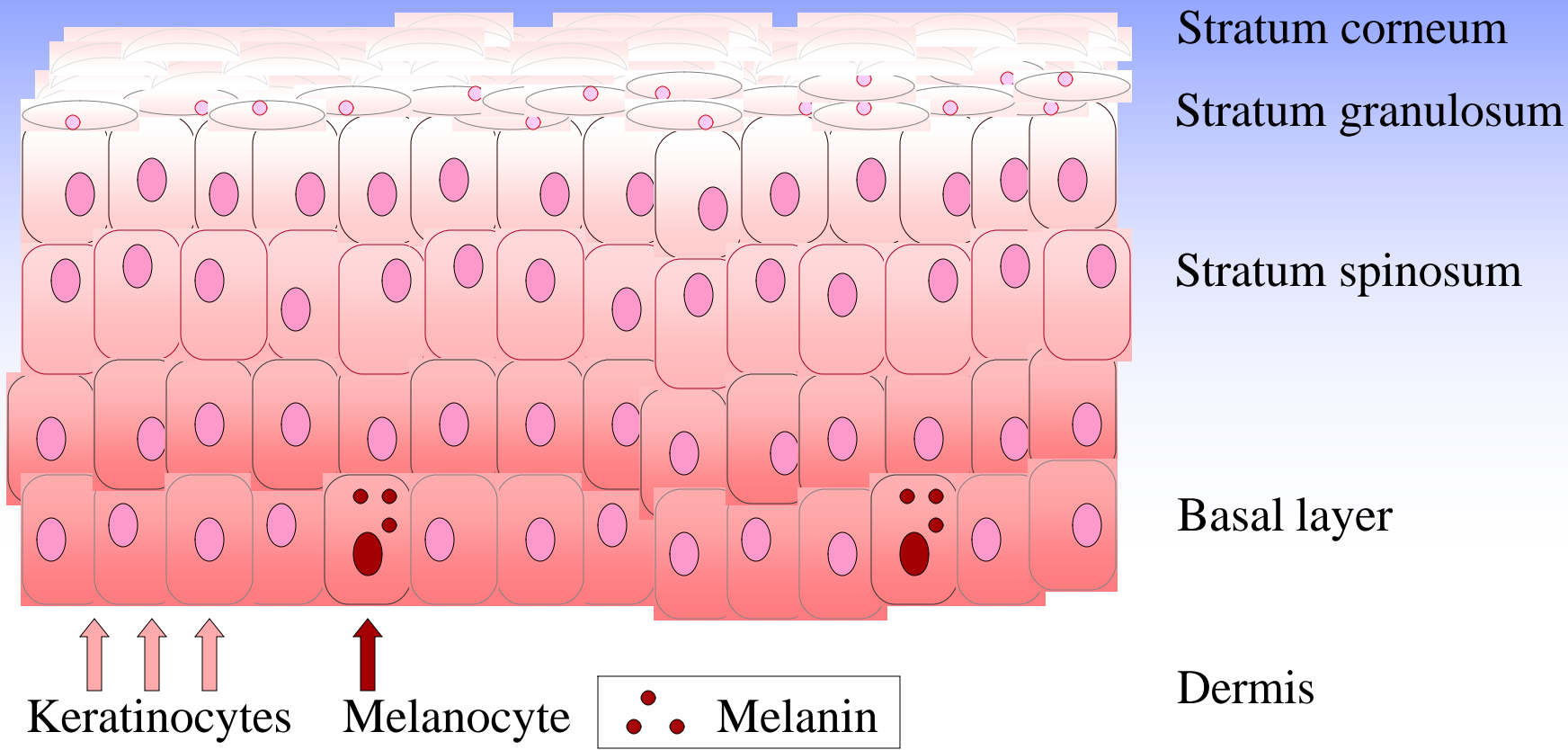
16 Case-Control Studies of Sunscreen Use and Melanoma



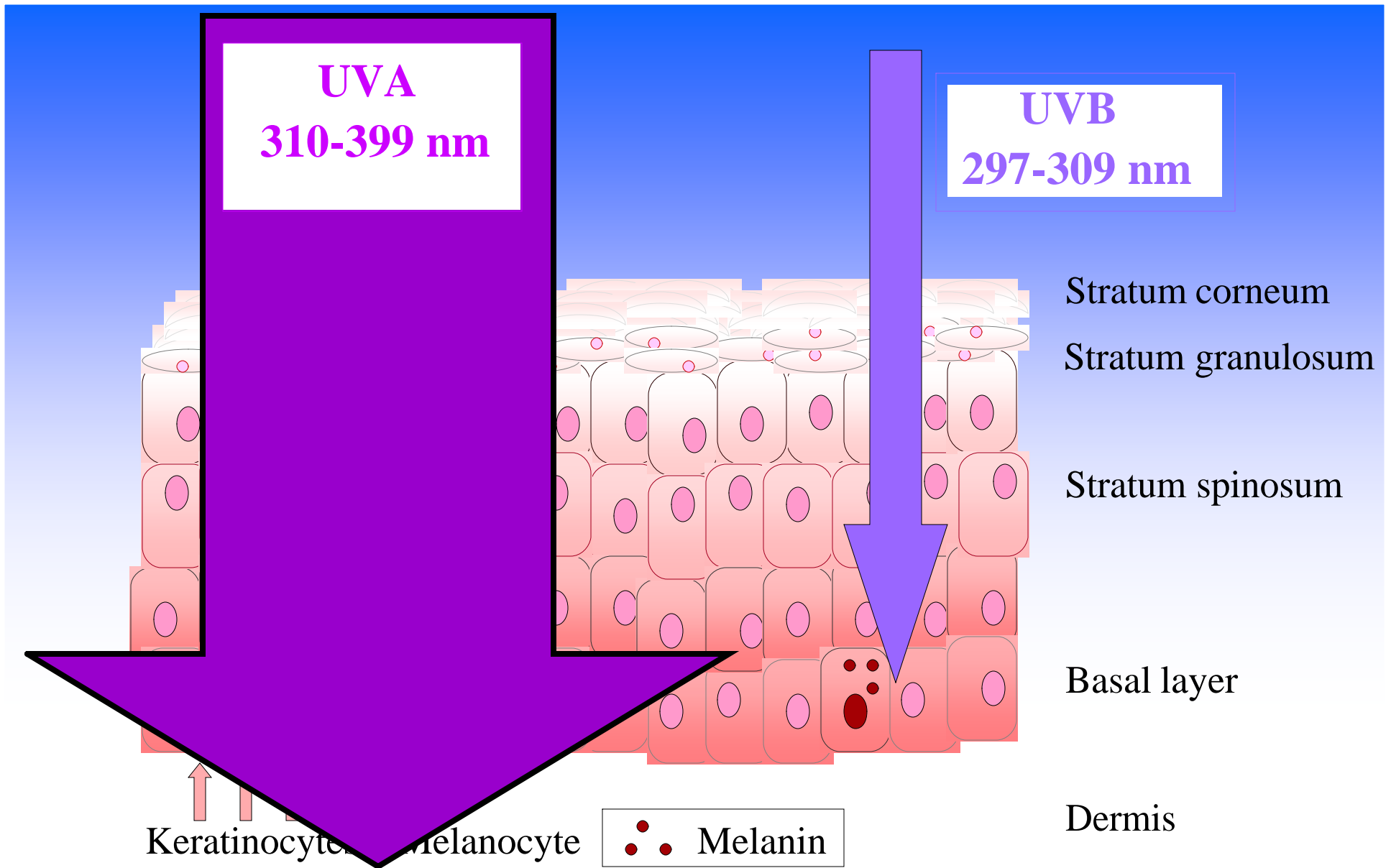
Odds Ratios for malignant melanoma associated with sunscreen use
(4 lower, 5 not statistically significant, 7 elevated)



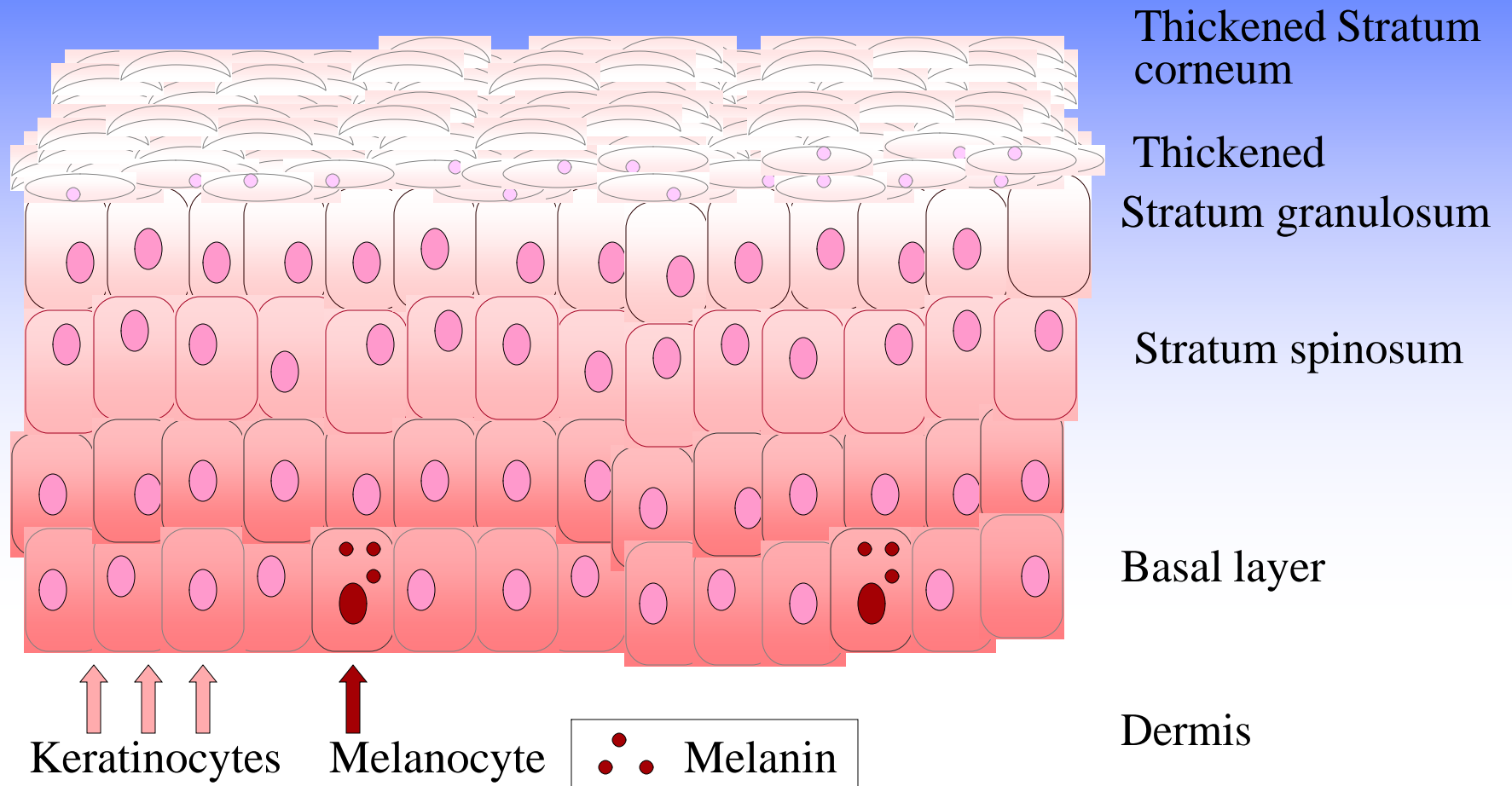
Source: Gorham ED, Mohr SB, Garland CF, Chaplin G, Garland FC. Do sunscreens increase risk of melanoma in populations residing at higher latitudes? *Ann Epidemiol.* 2007;17:956-63.



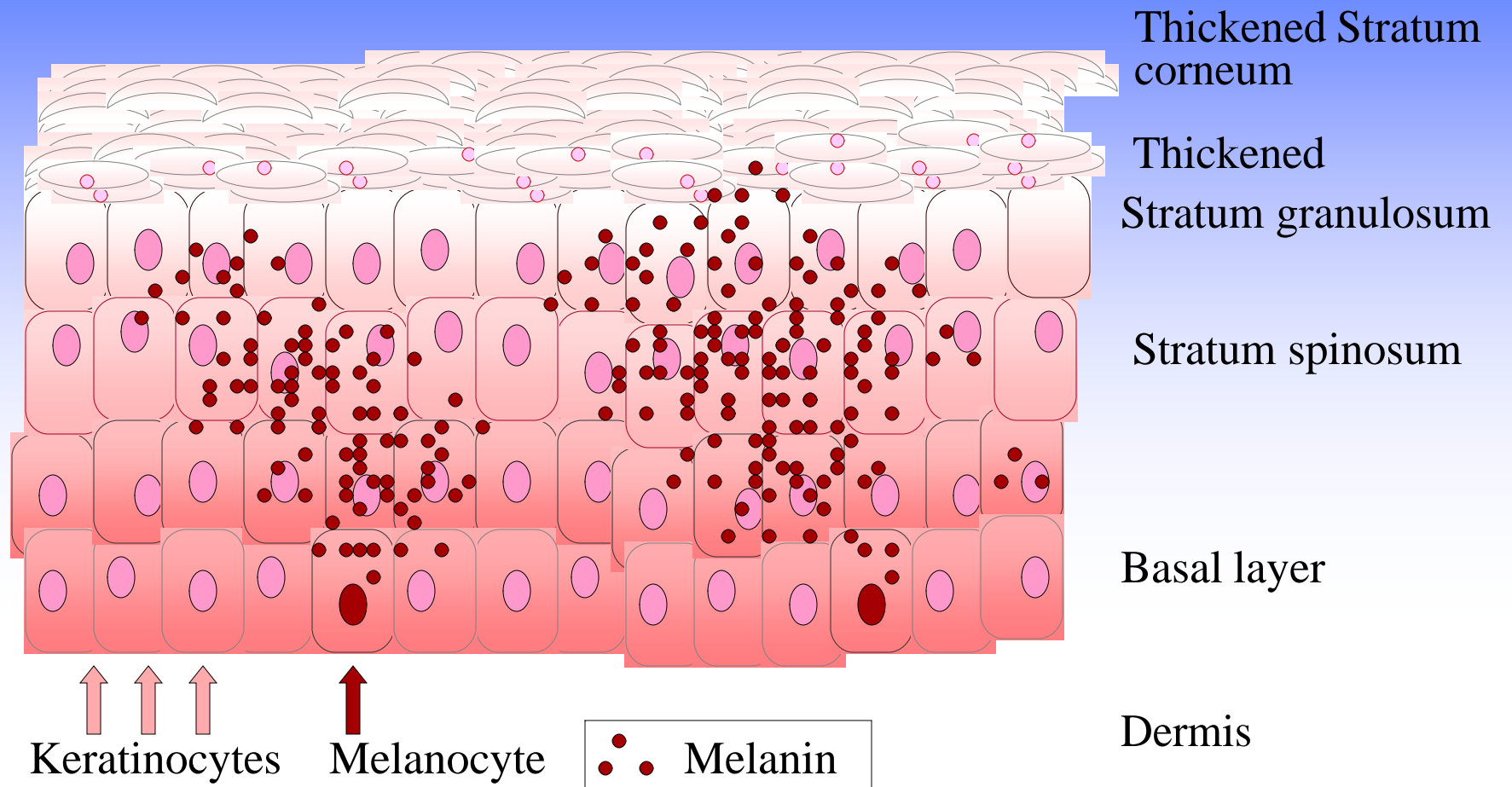
Human Photoprotective Response



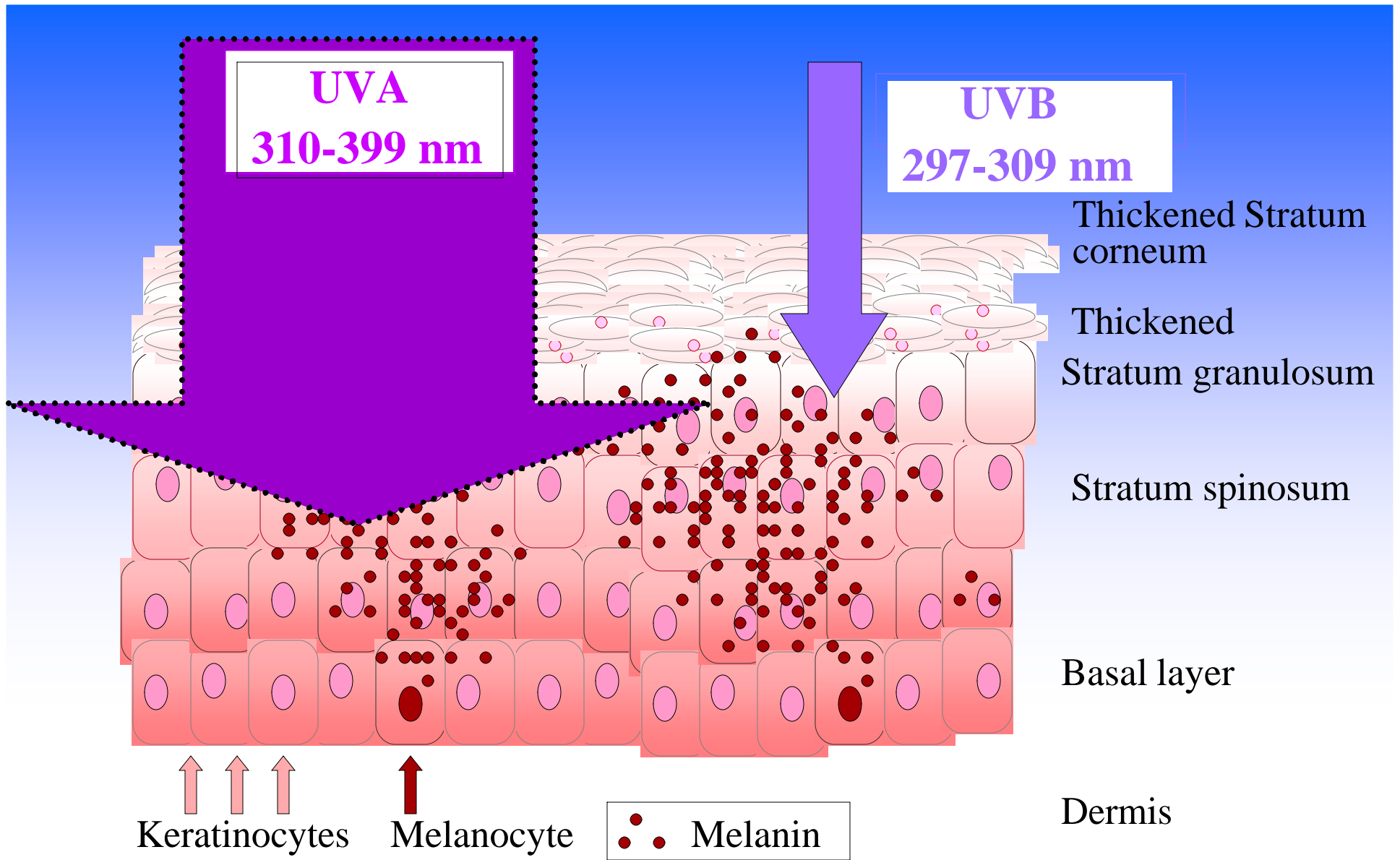
Human Photoprotective Response



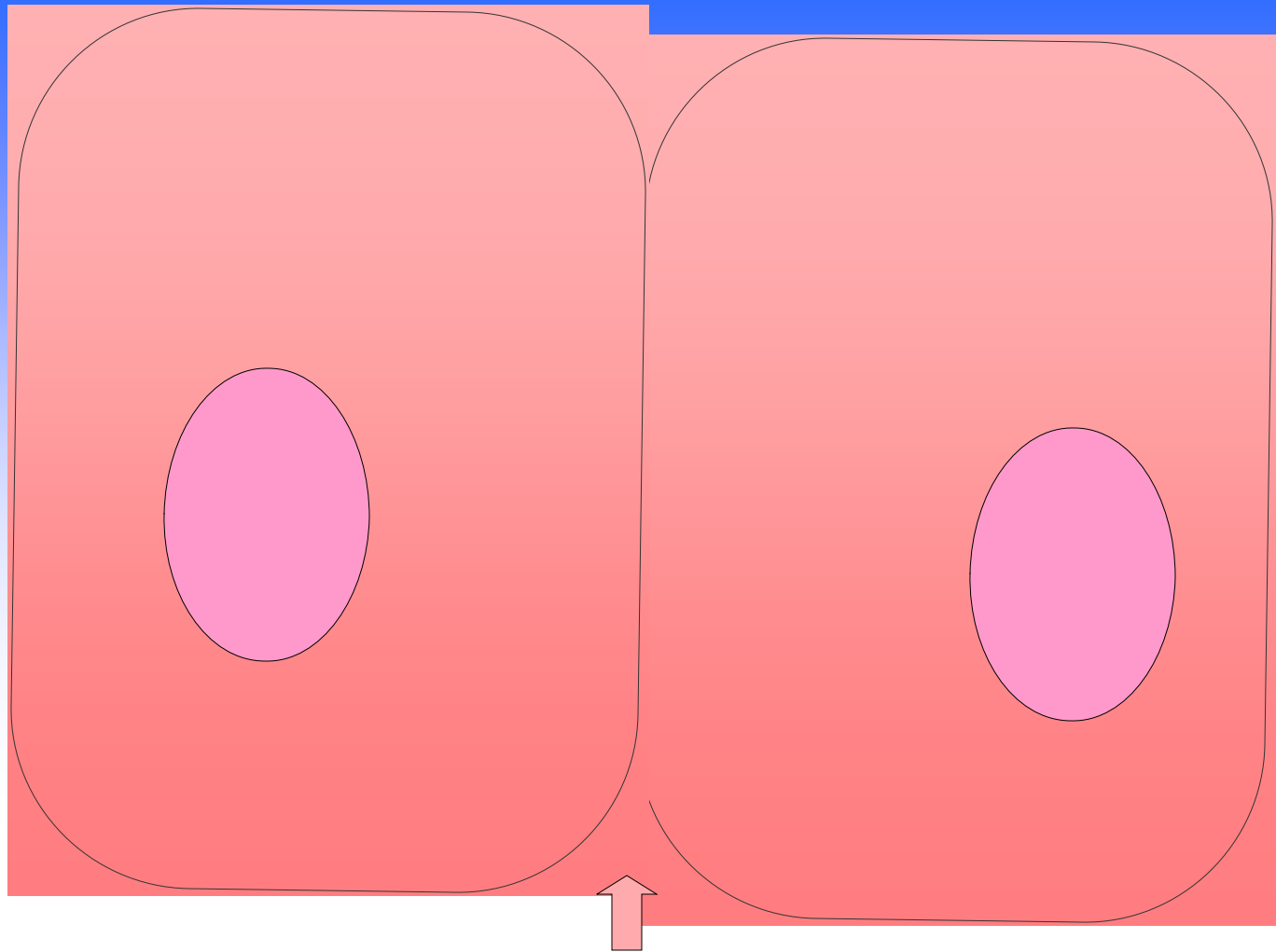
Human Photoprotective Response



Human Photoprotective Response



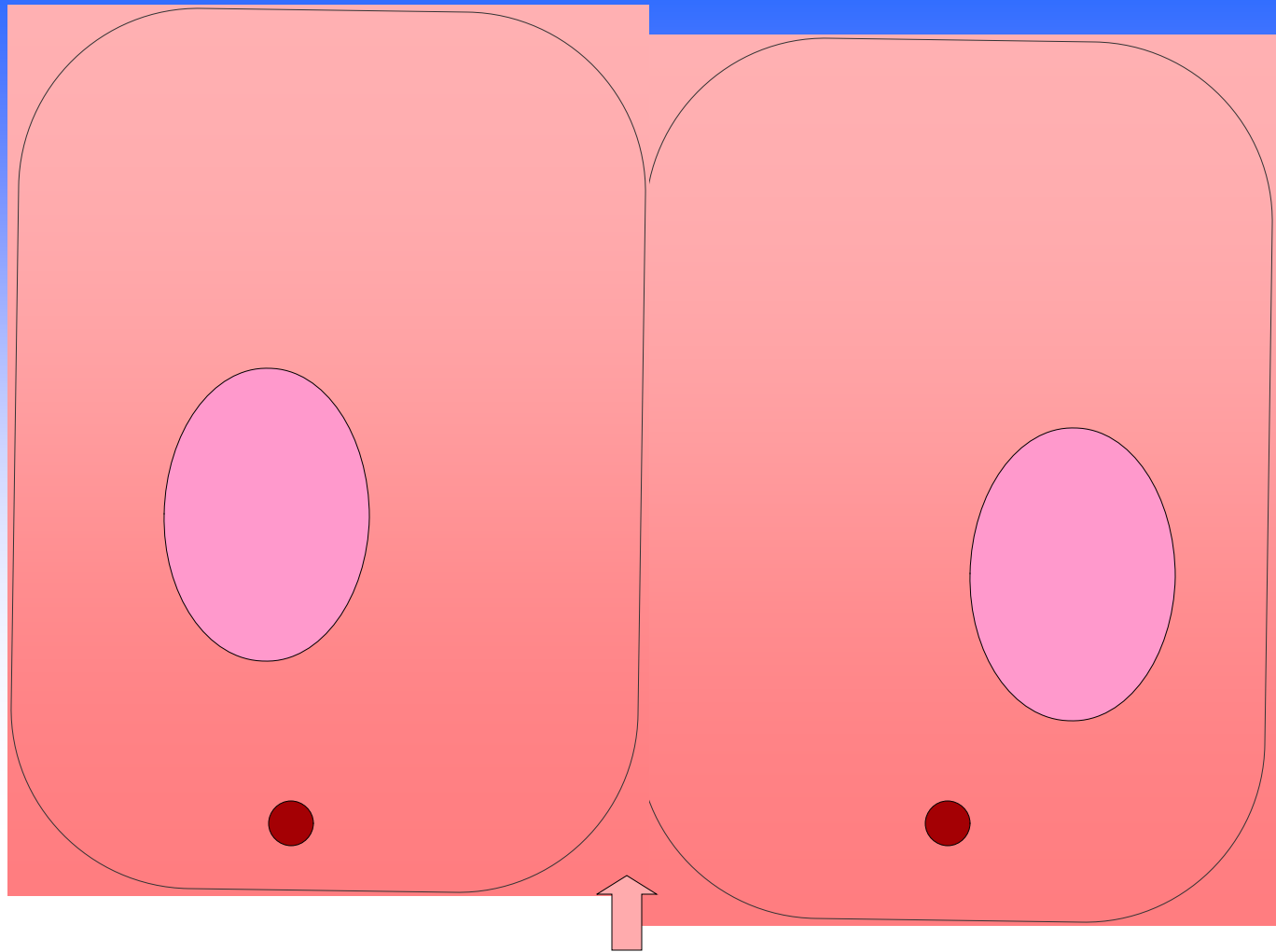
Human Photoprotective Response



● **Melanosome**

Keratinocytes

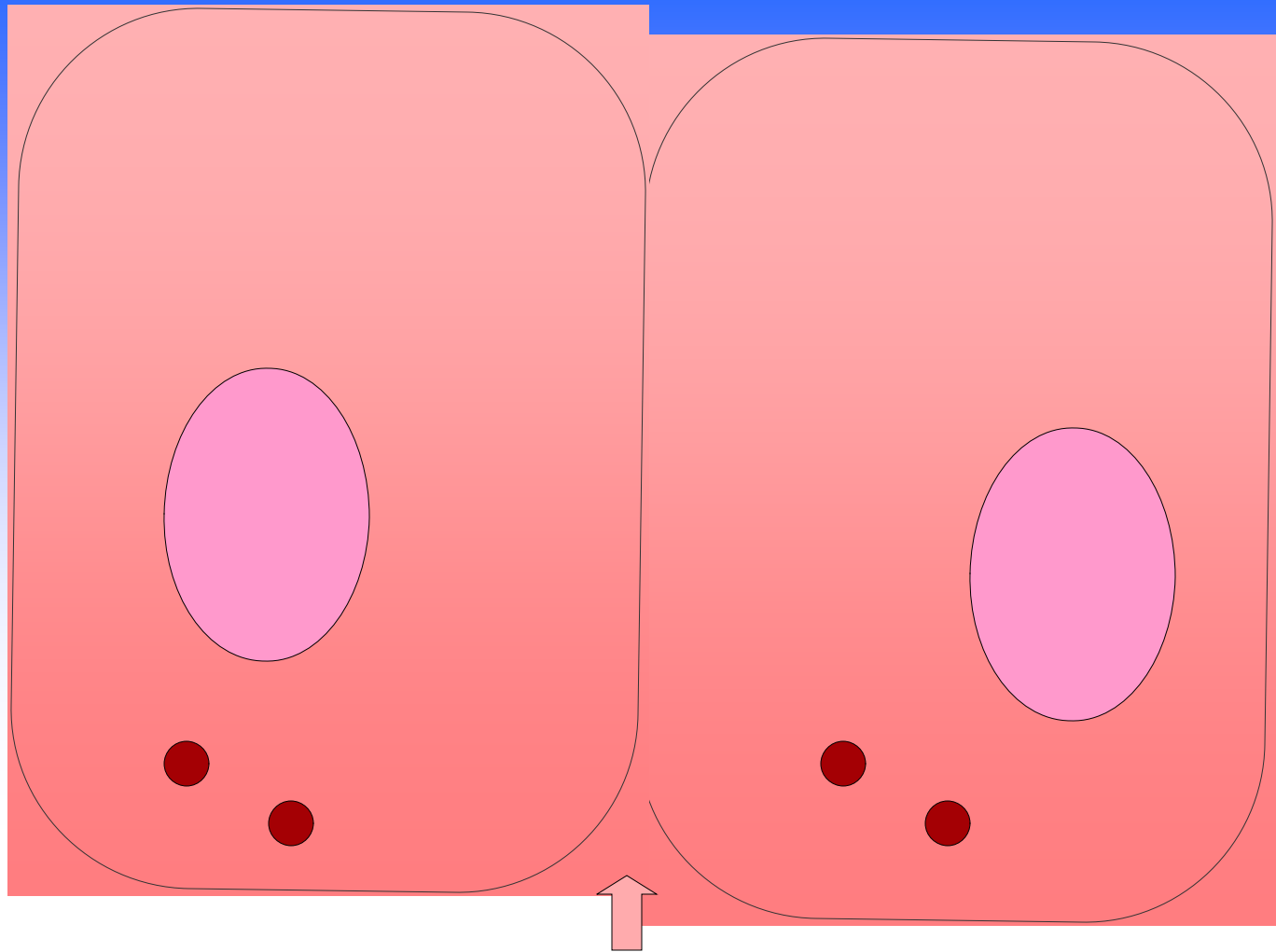
Melanosome migration in response to UV



● Melanosome

Keratinocytes

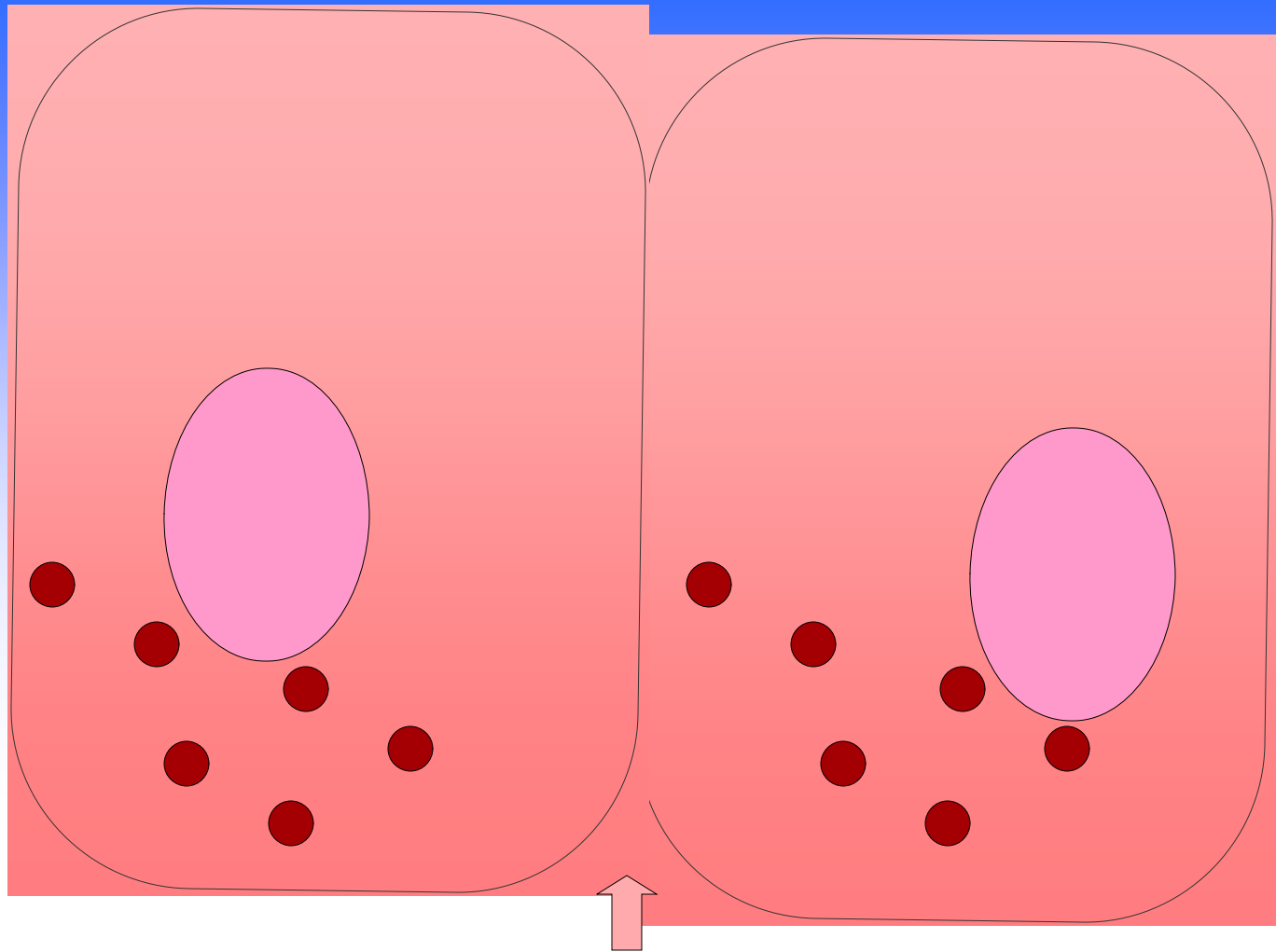
Melanosome migration in response to UV



● Melanosome

Keratinocytes

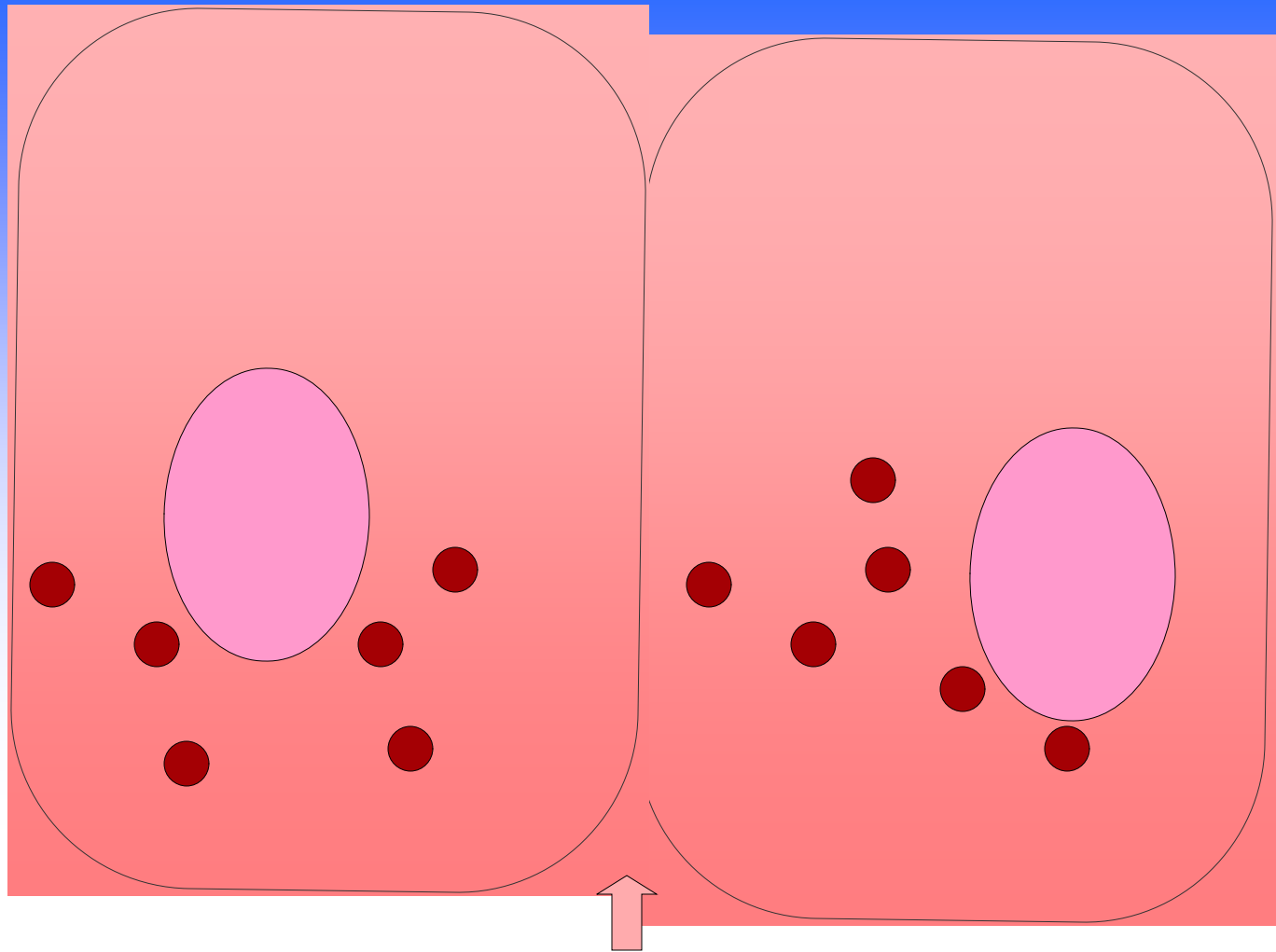
Melanosome migration in response to UV



● Melanosome

Keratinocytes

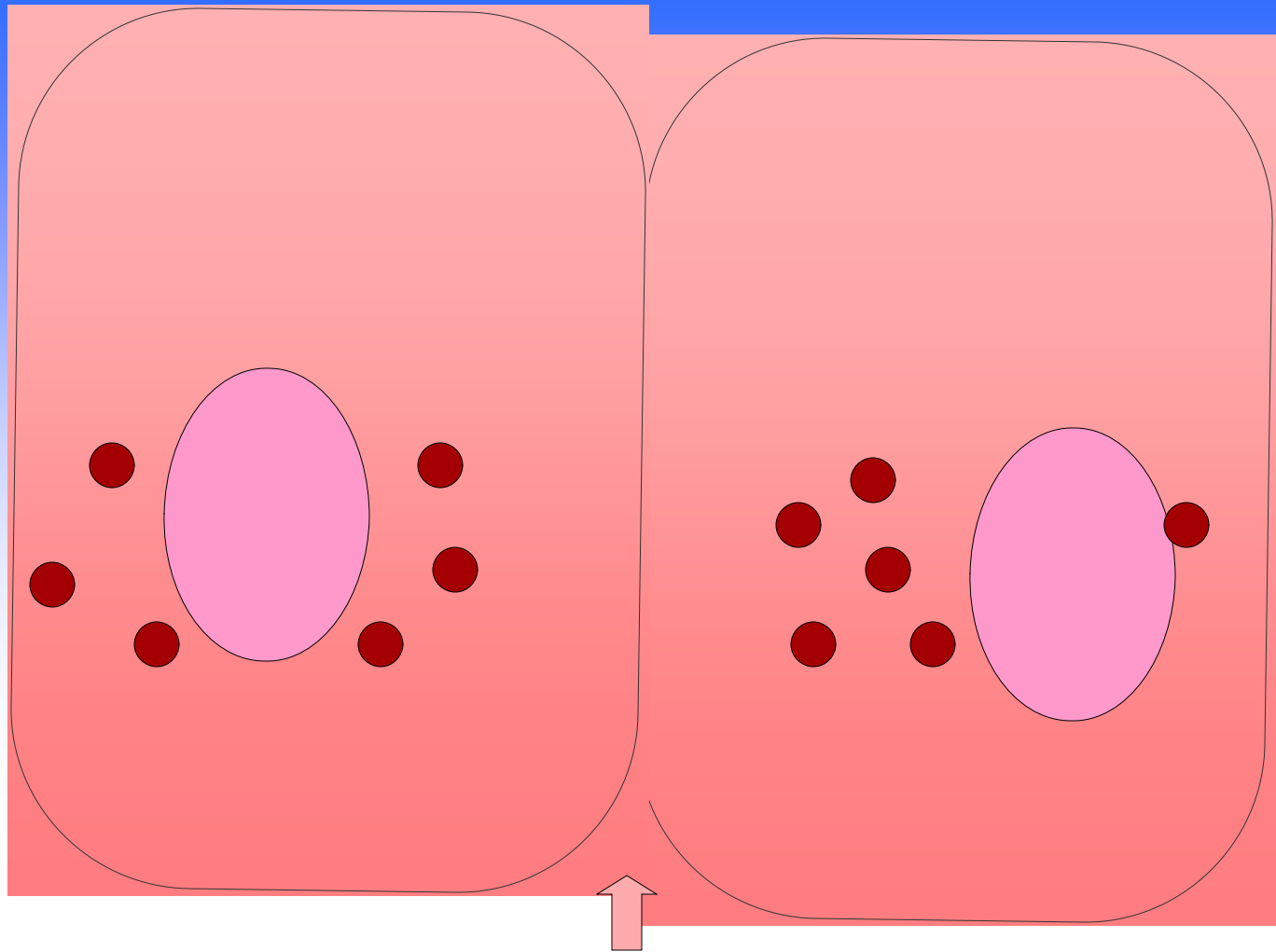
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● Melanosome

Keratinocytes

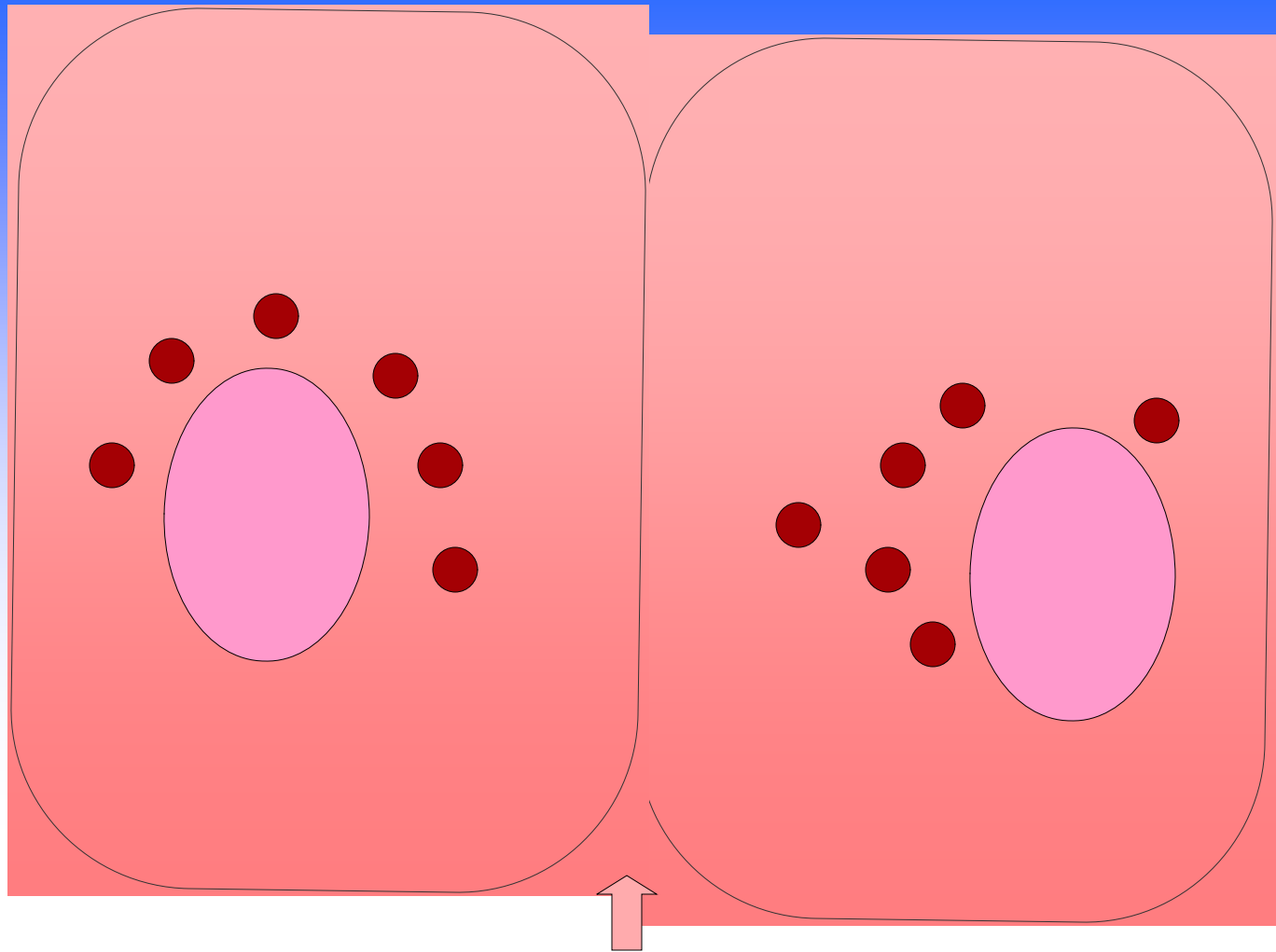
Melanosome migration in response to UV



● Melanosome

Keratinocytes

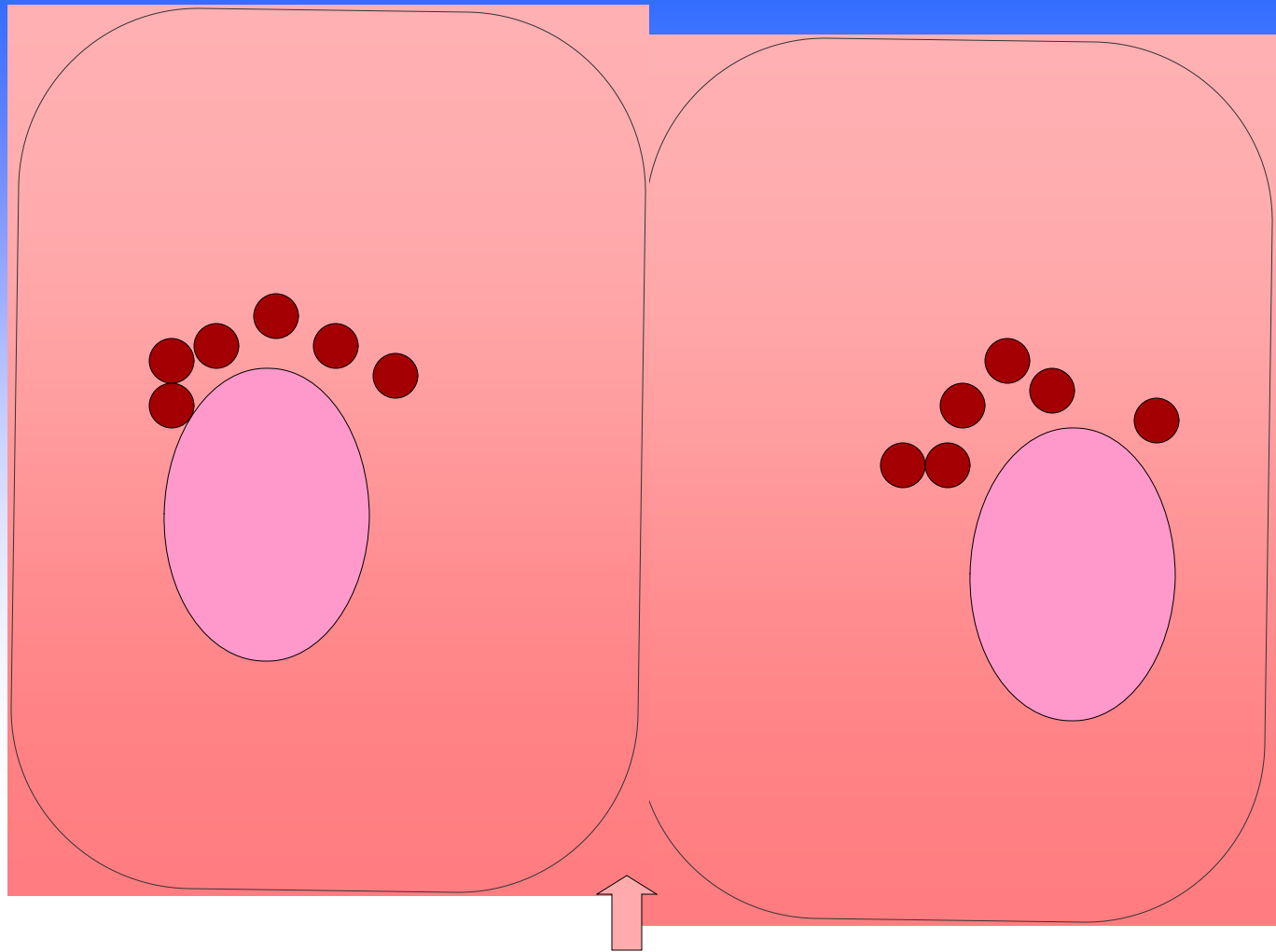
Melanosome migration in response to UV



● Melanosome

Keratinocytes

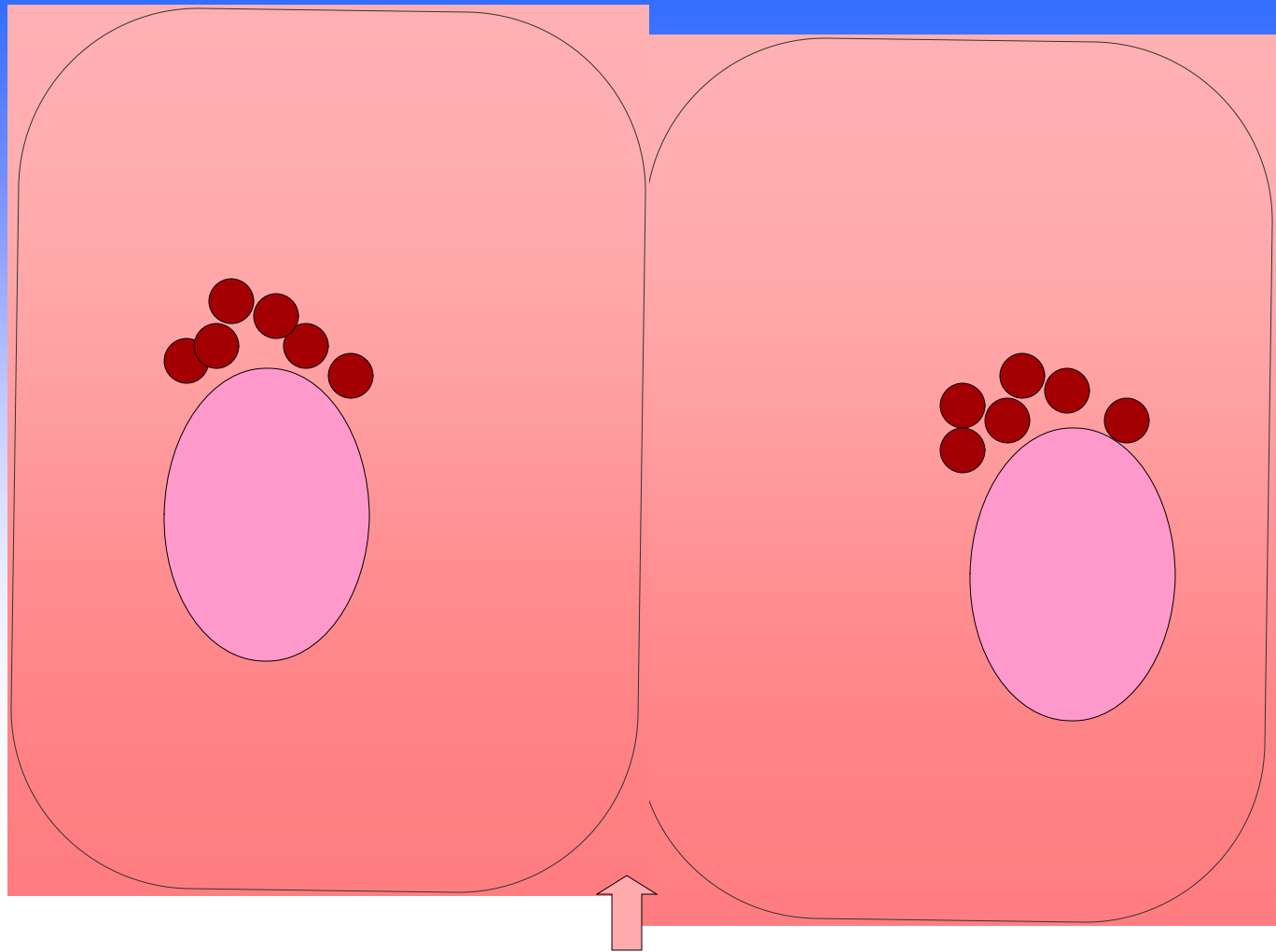
Melanosome migration in response to UV



● Melanosome

↑ Keratinocytes

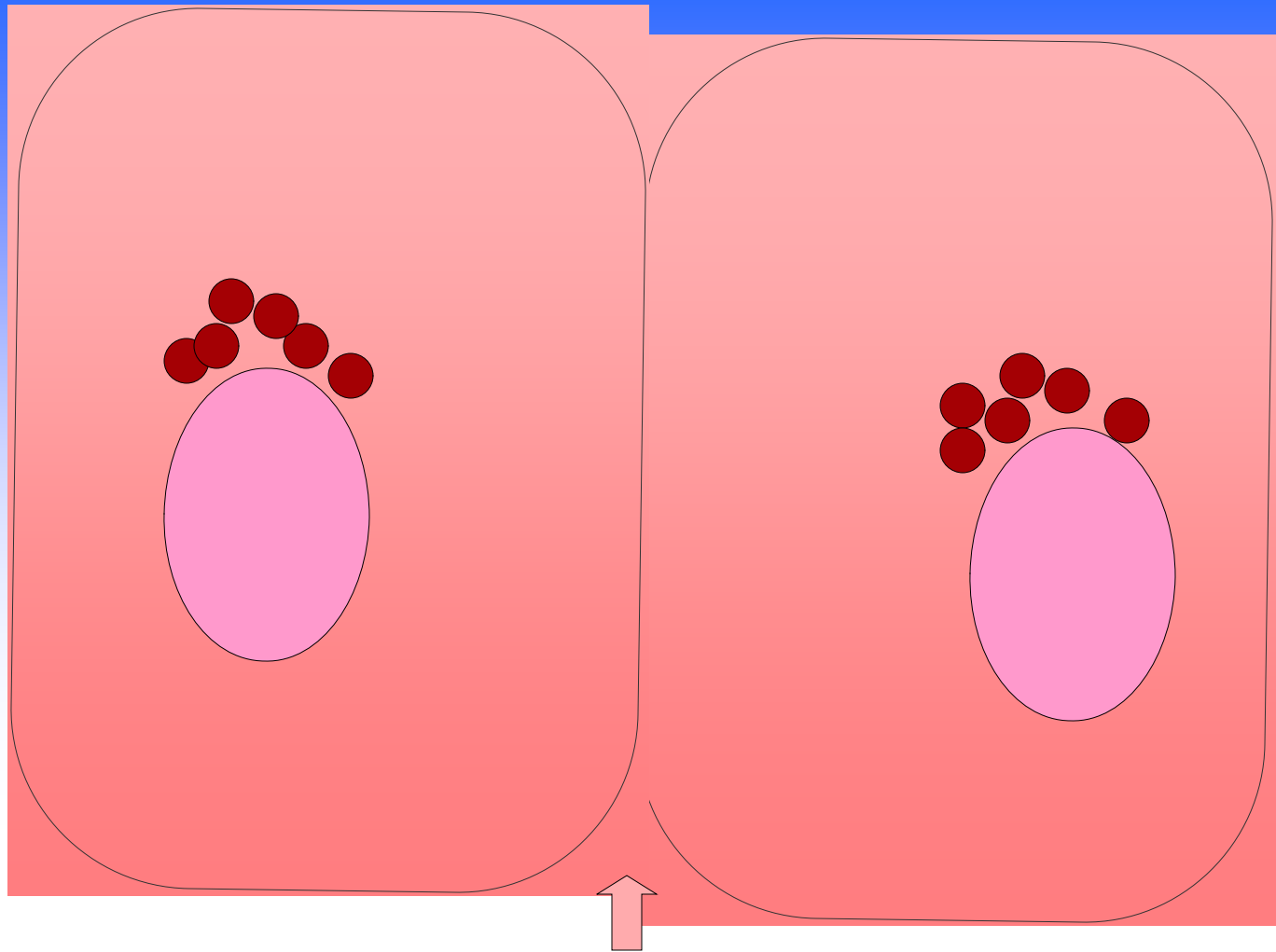
Melanosome migration in response to UV



● Melanosome

Keratinocytes

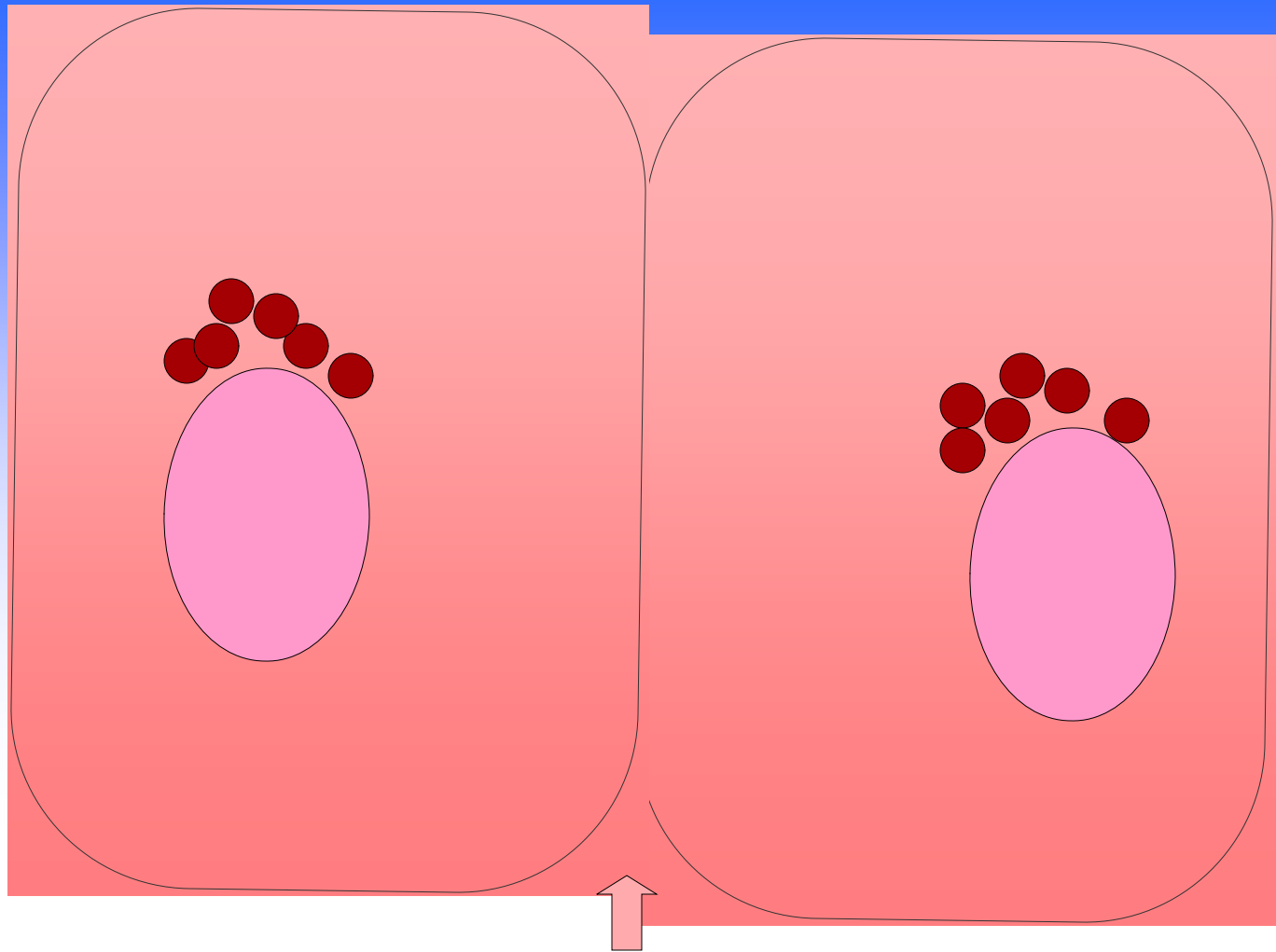
Melanosome migration in response to UV



● Melanosome

Keratinocytes

Melanosome migration in response to UV

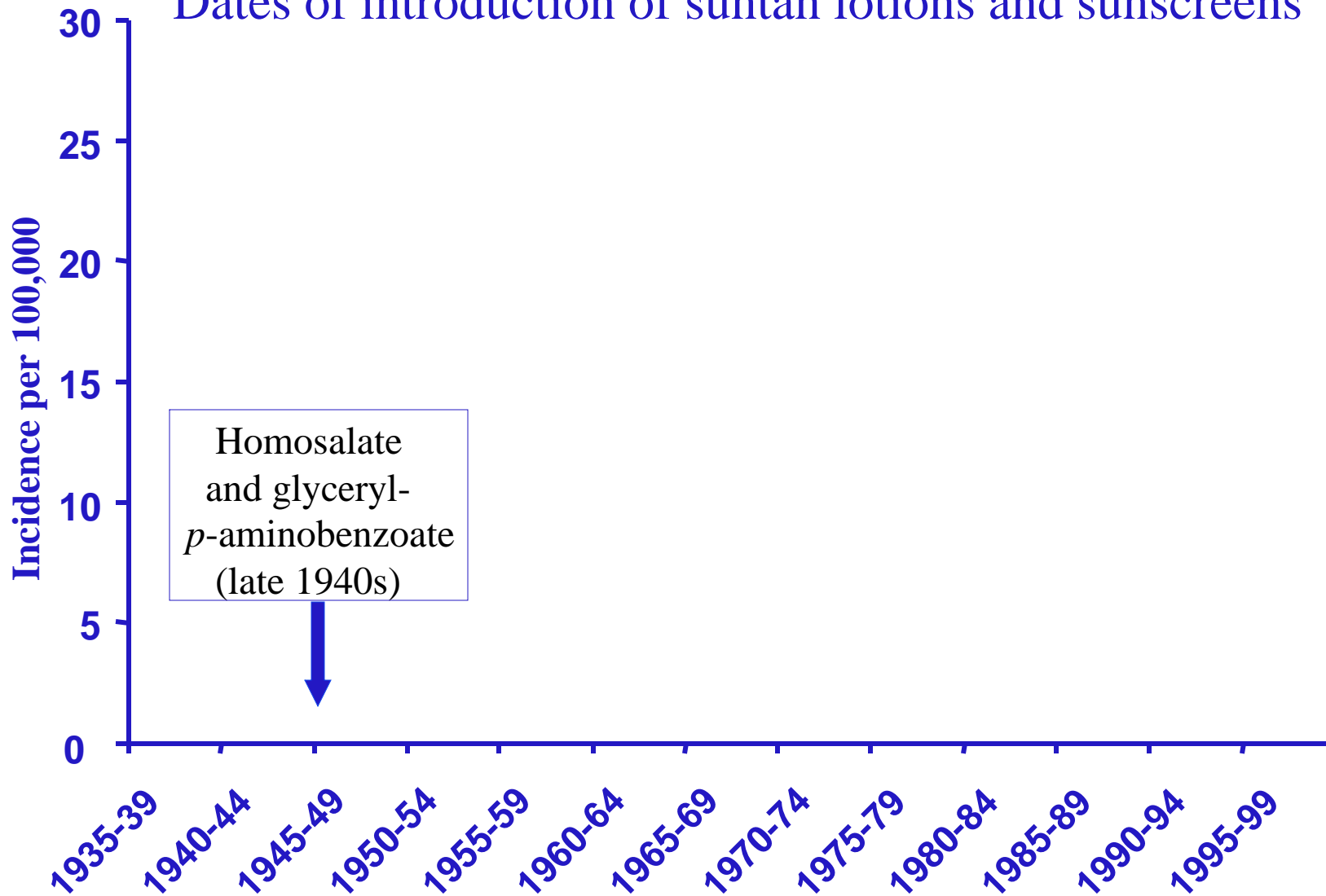


● Melanosome

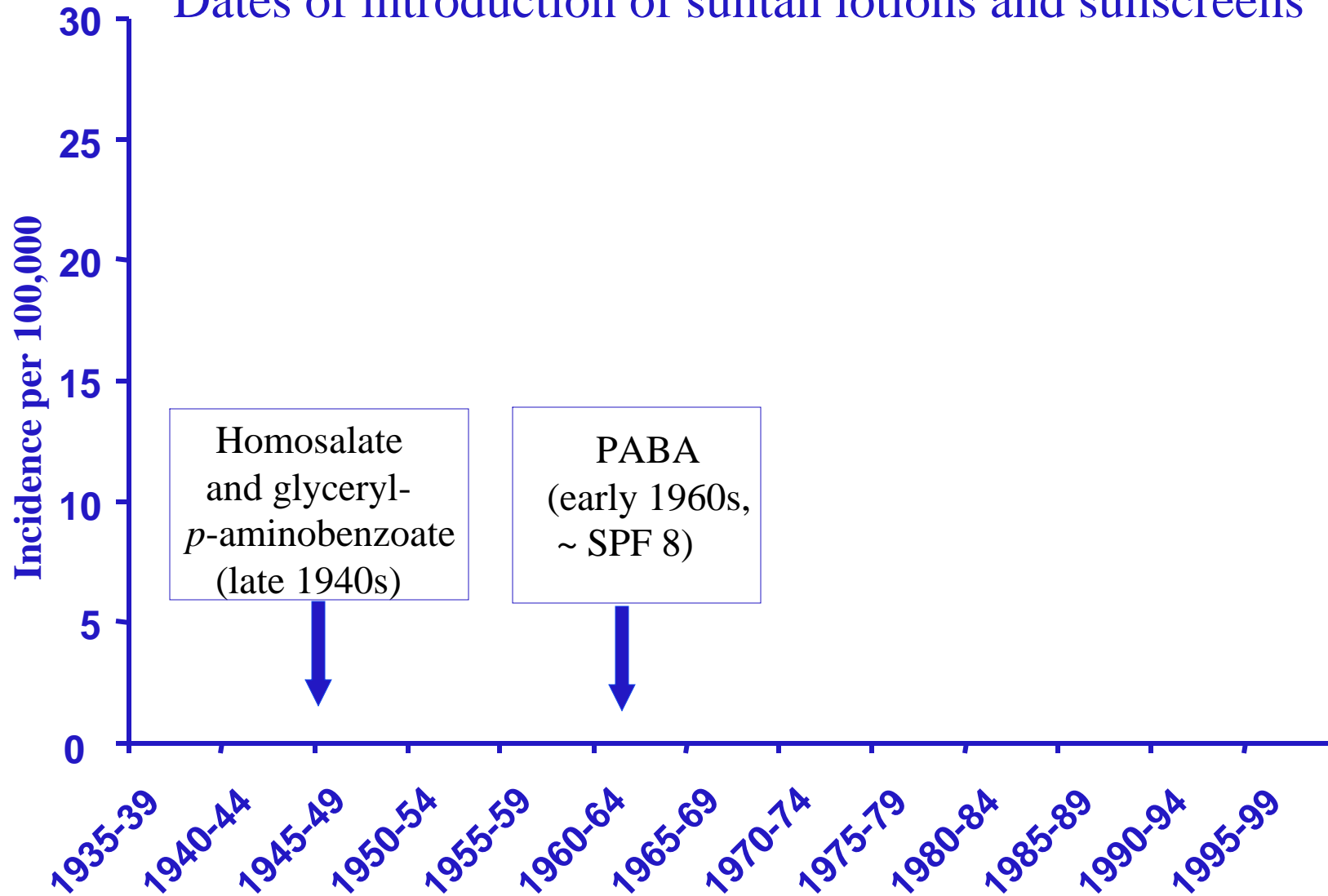
Keratinocytes

Melanosome migration in response to UV

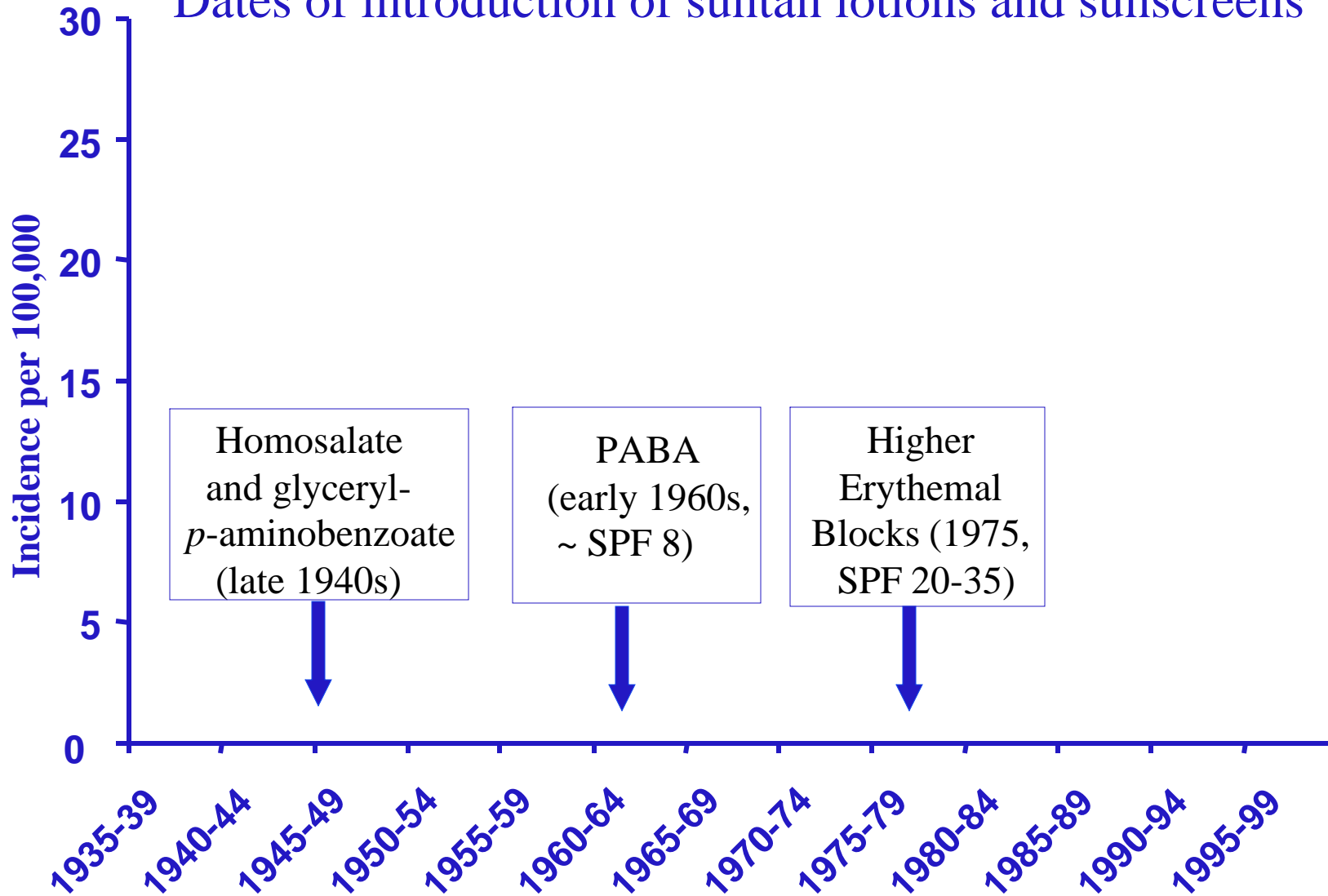
Dates of introduction of suntan lotions and sunscreens



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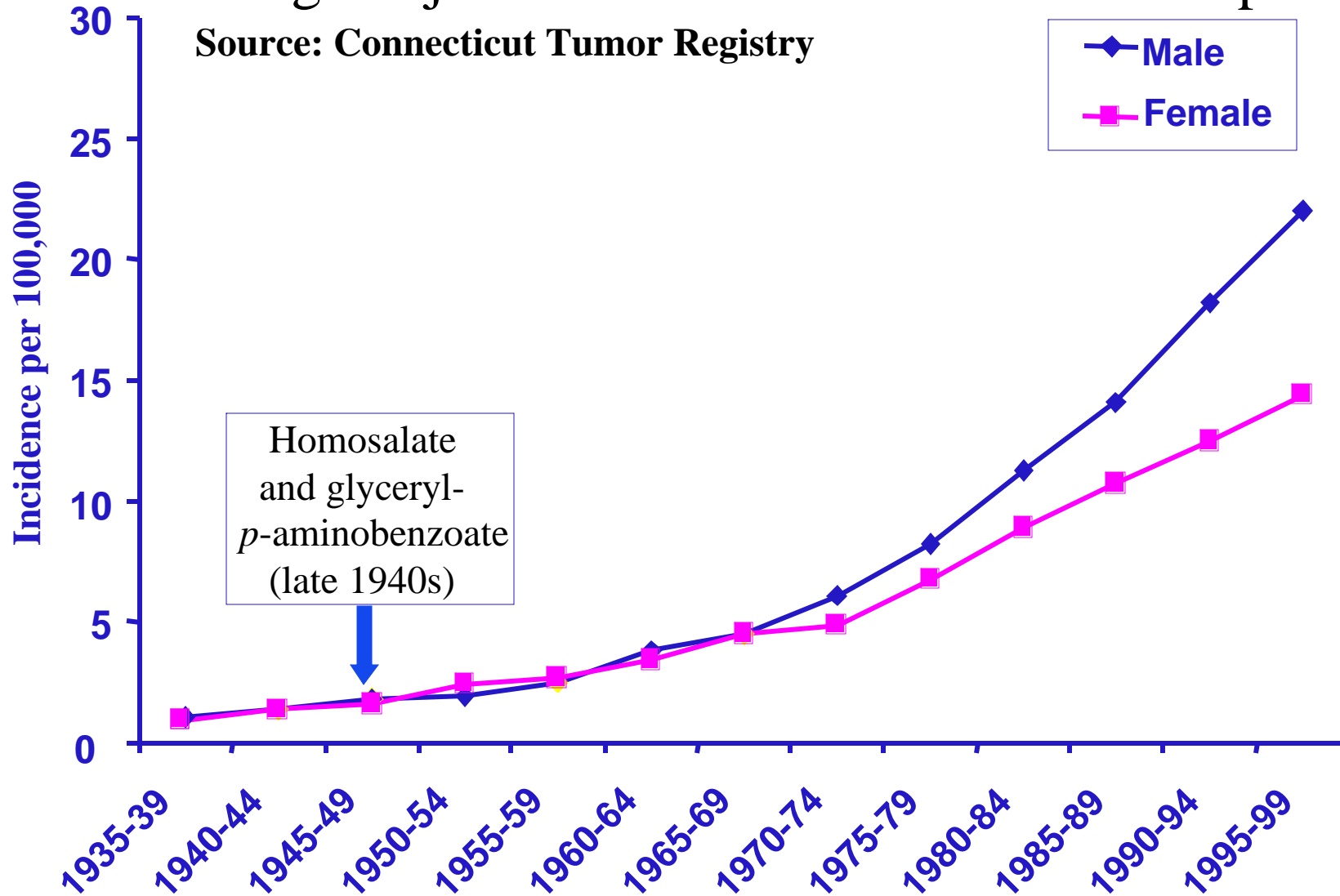


Dates of introduction of suntan lotions and sunscreens

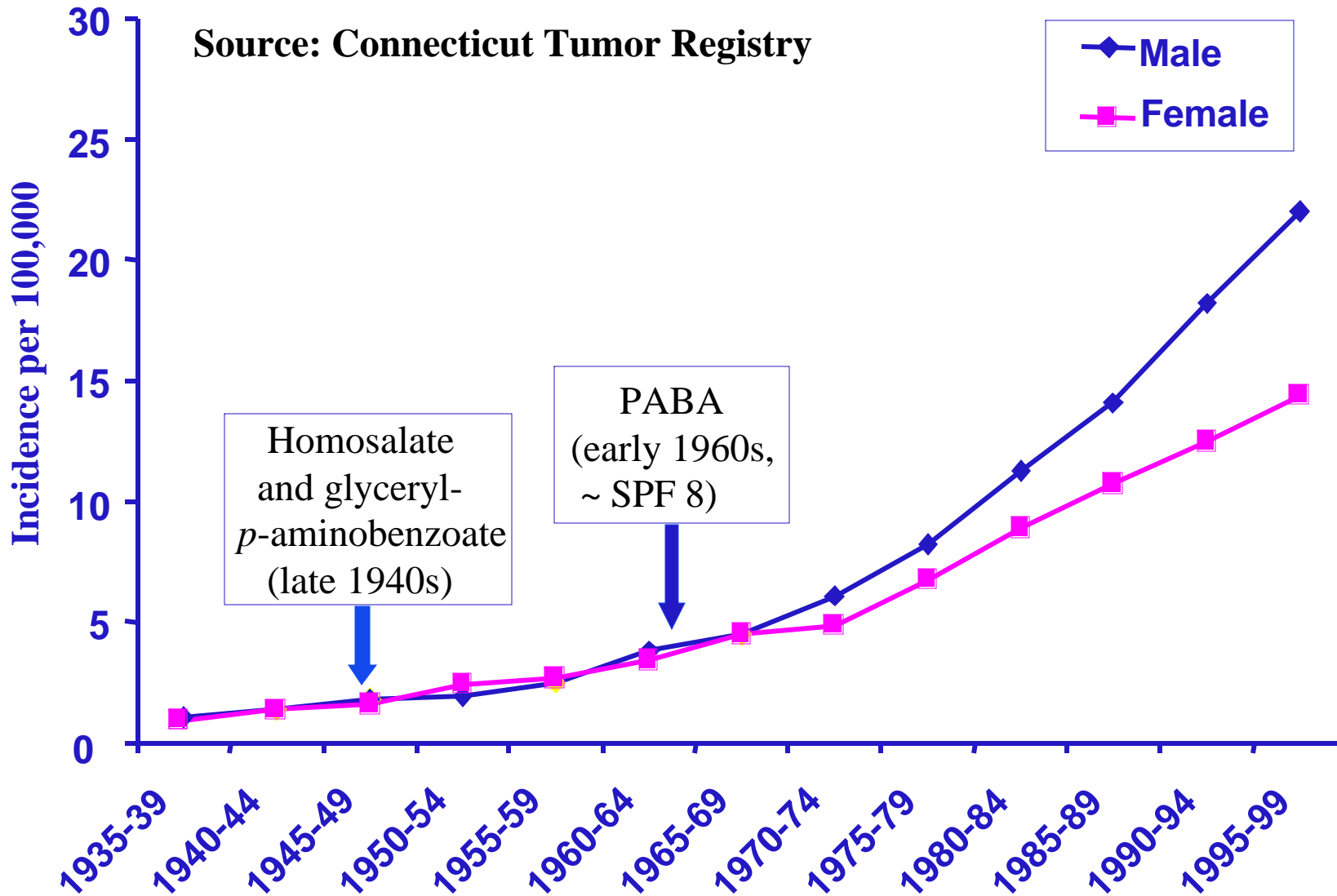


Dates of introduction of suntan lotions and sunscreens and age-adjusted melanoma incidence rates per 100,000

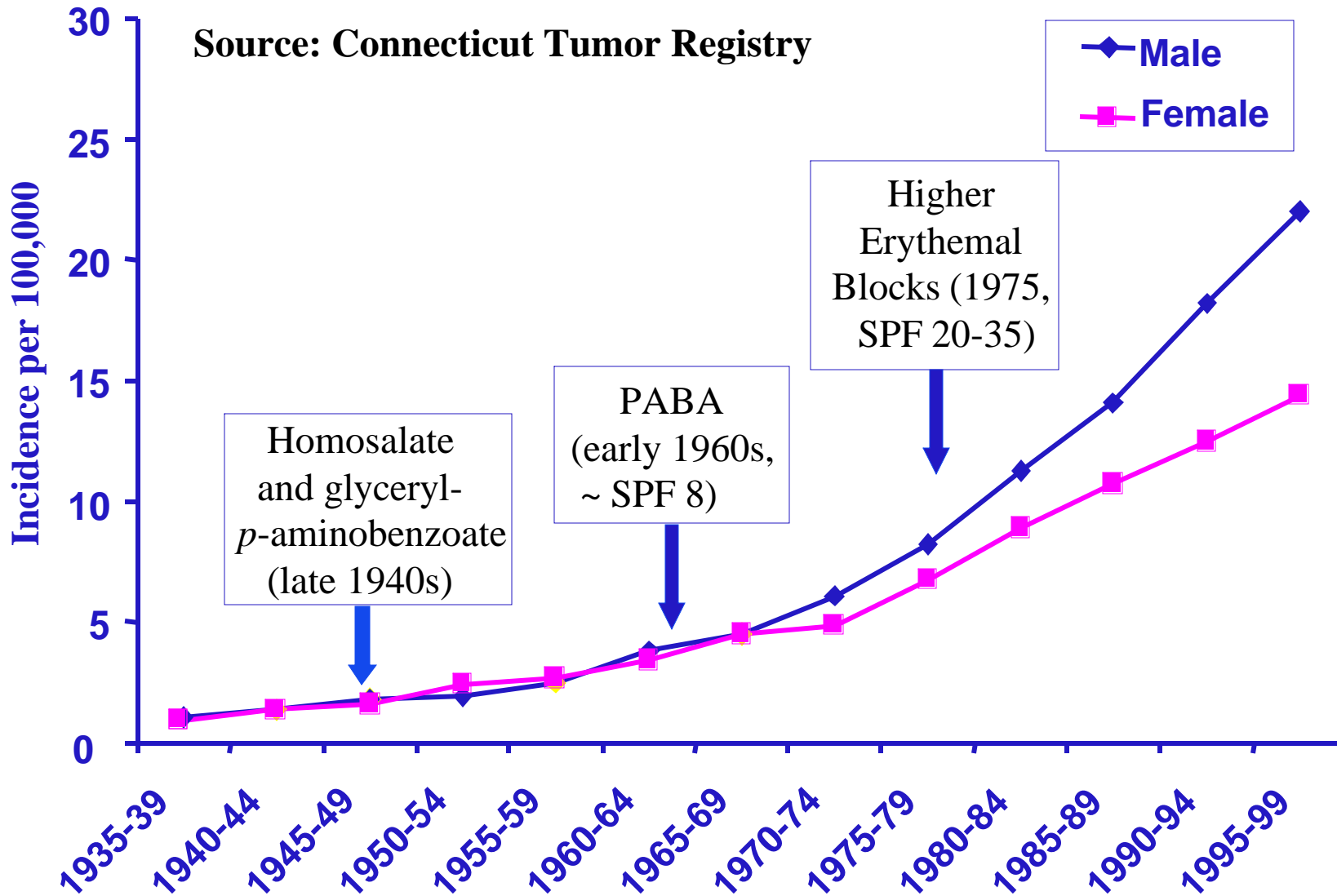
Source: Connecticut Tumor Registry



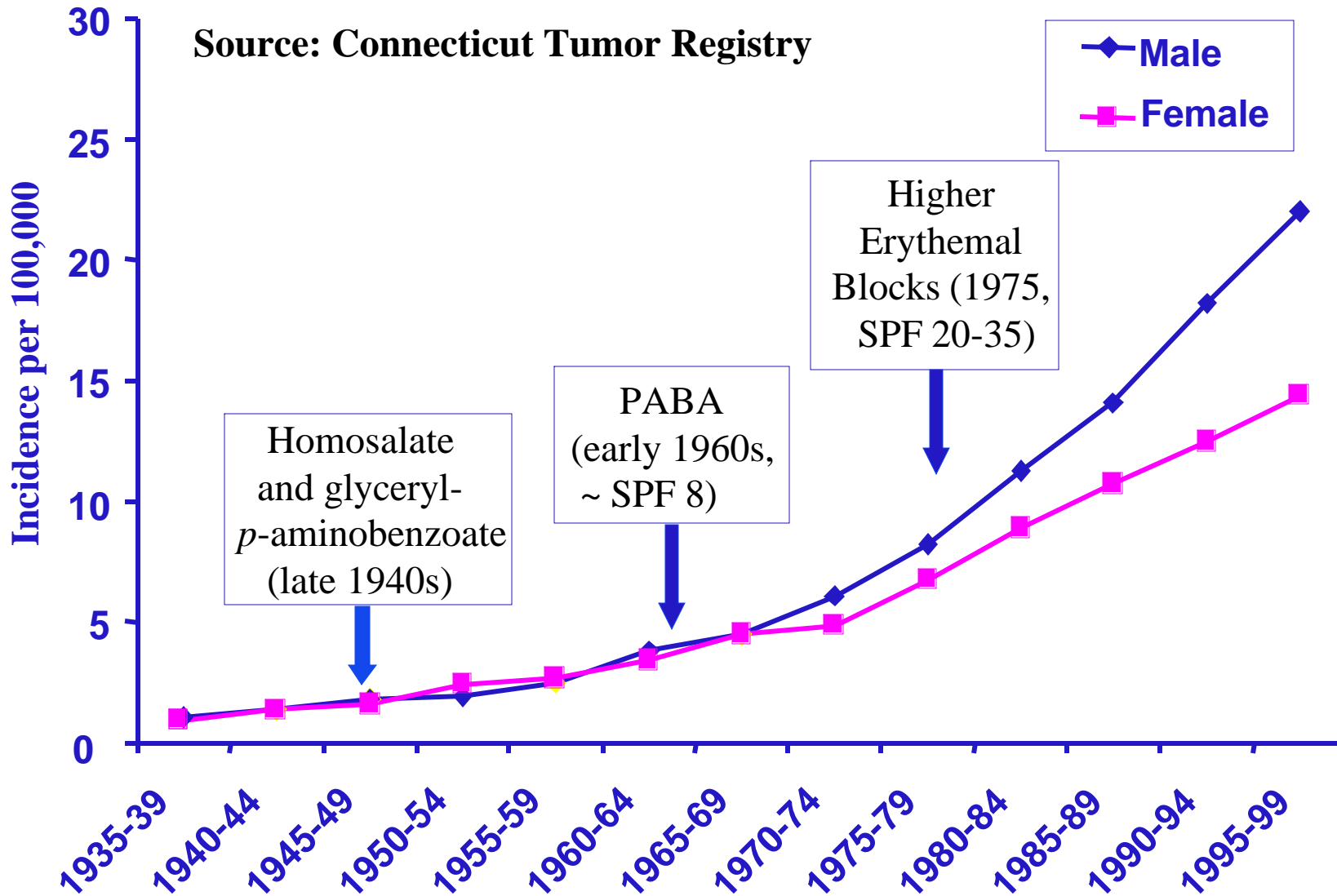
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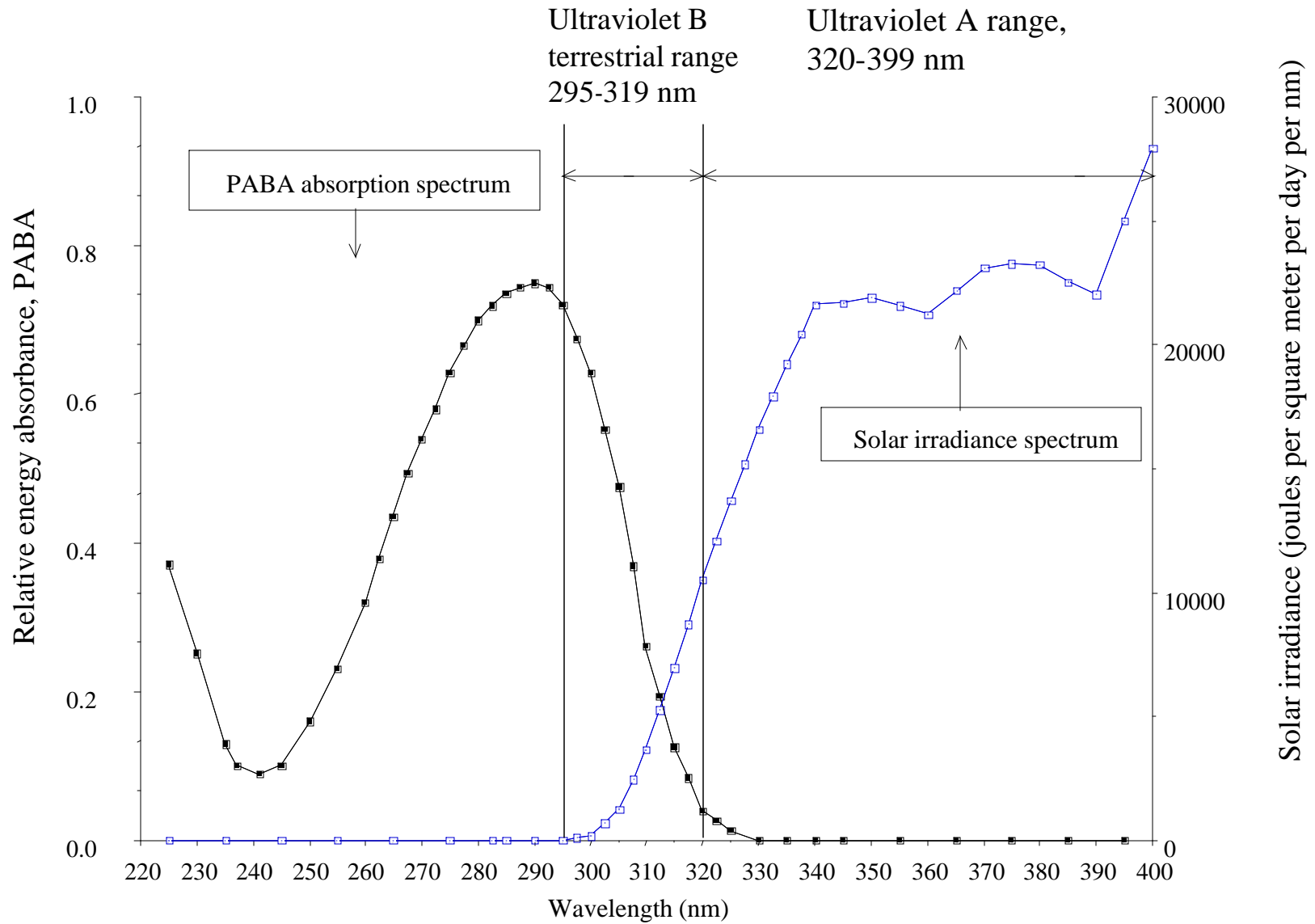


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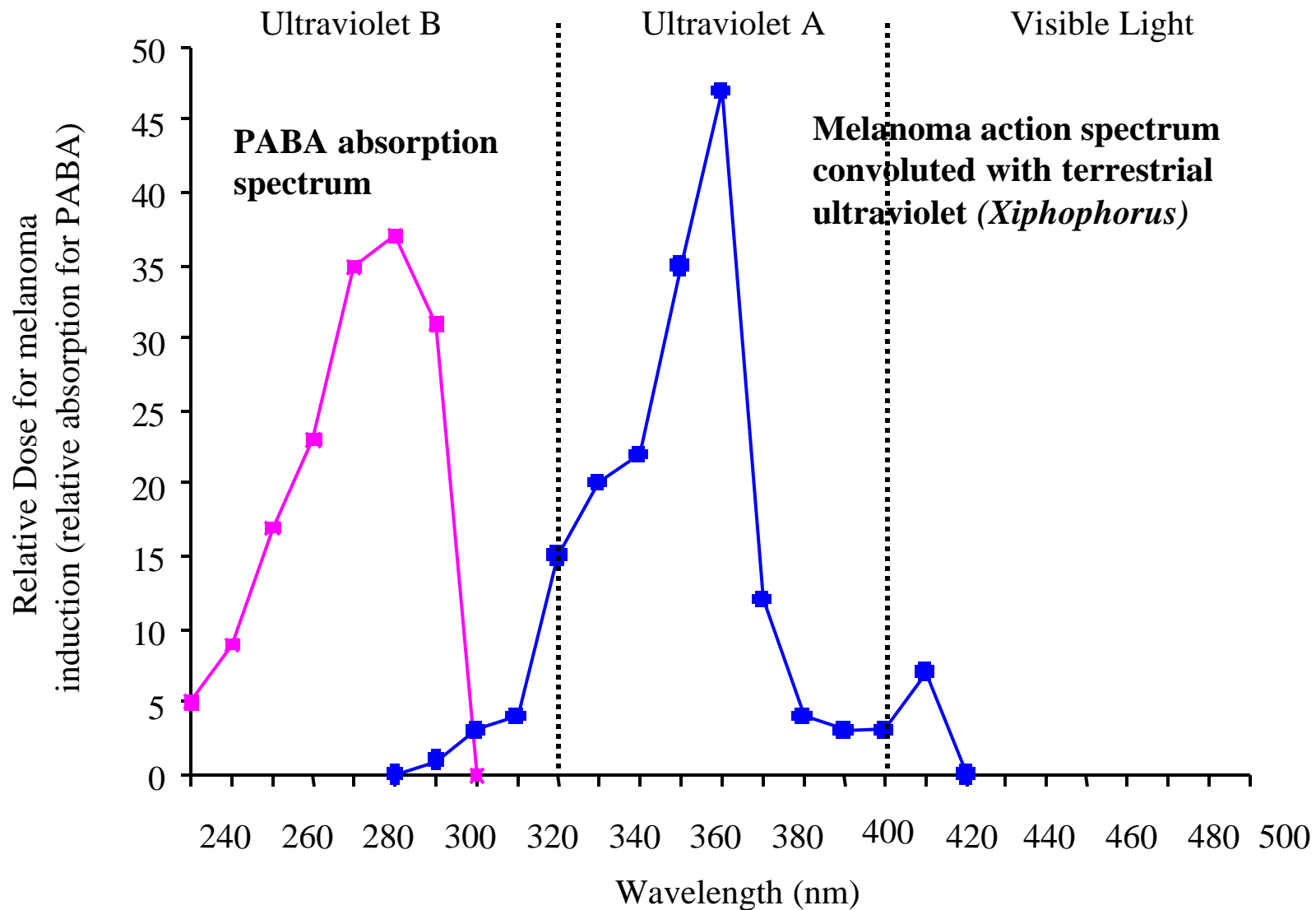


Dates of introduction of suntan lotions and sunscreens and age-adjusted melanoma incidence rates per 100,000

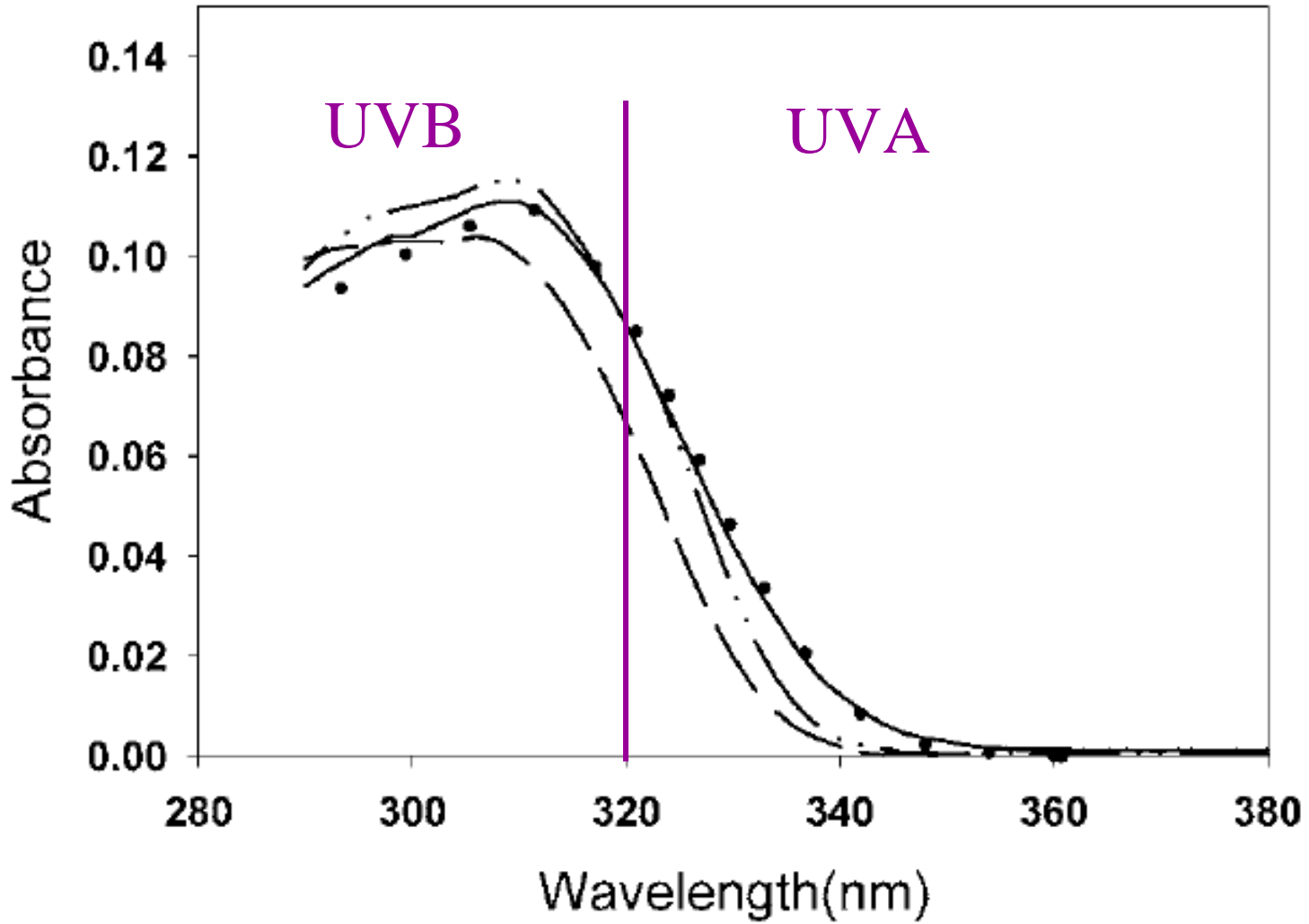




Solar ultraviolet irradiance and relative energy absorbance by para-aminobenzoic acid

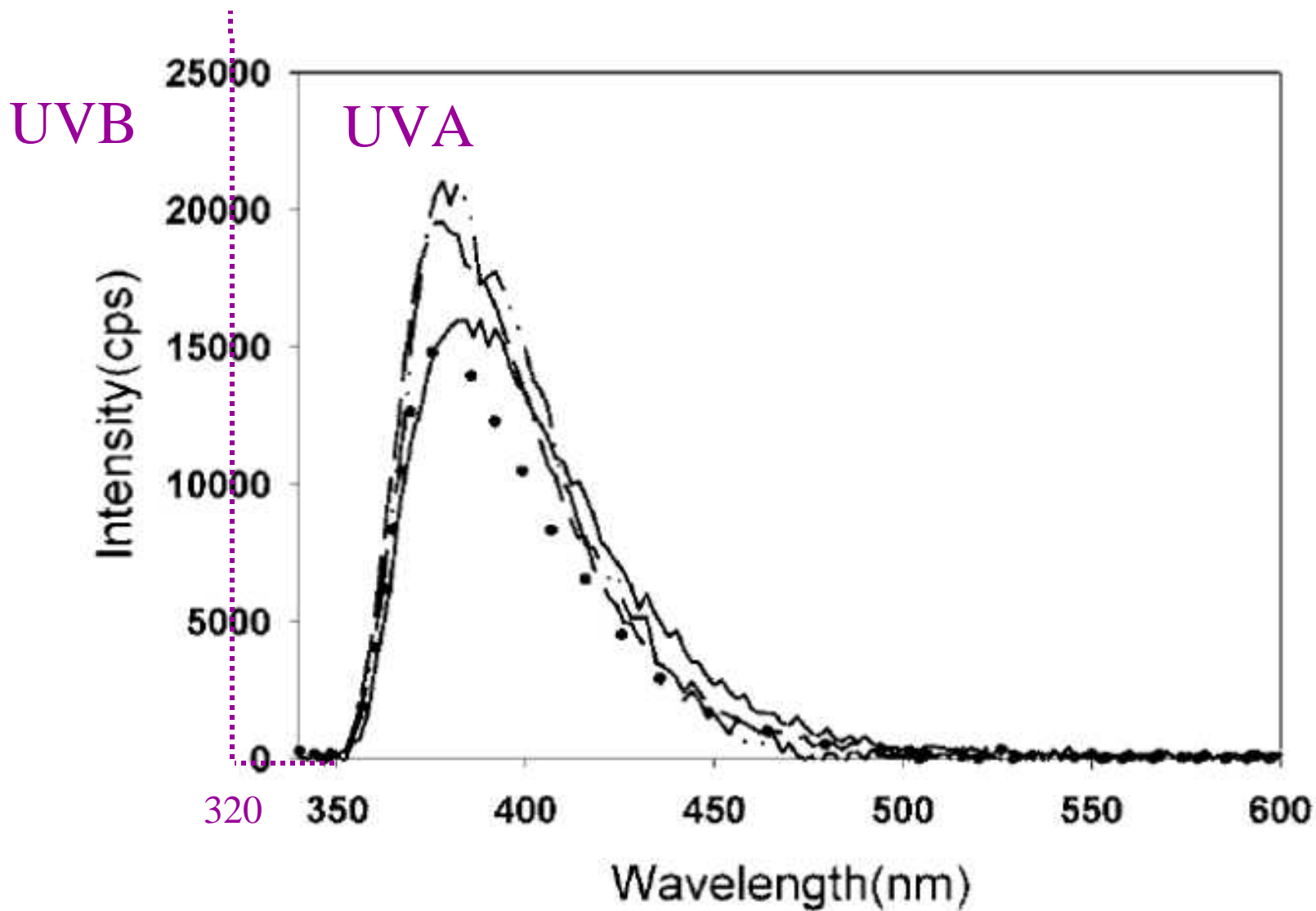


Relative absorption spectrum of PABA sunscreen agent and fish melanoma action spectrum
 Source: Setlow RB, Woodhead AD. Temporal Changes in the incidence of melanoma: explanation from an action spectrum. *Mutation Res* 1994; 307: 365-74.



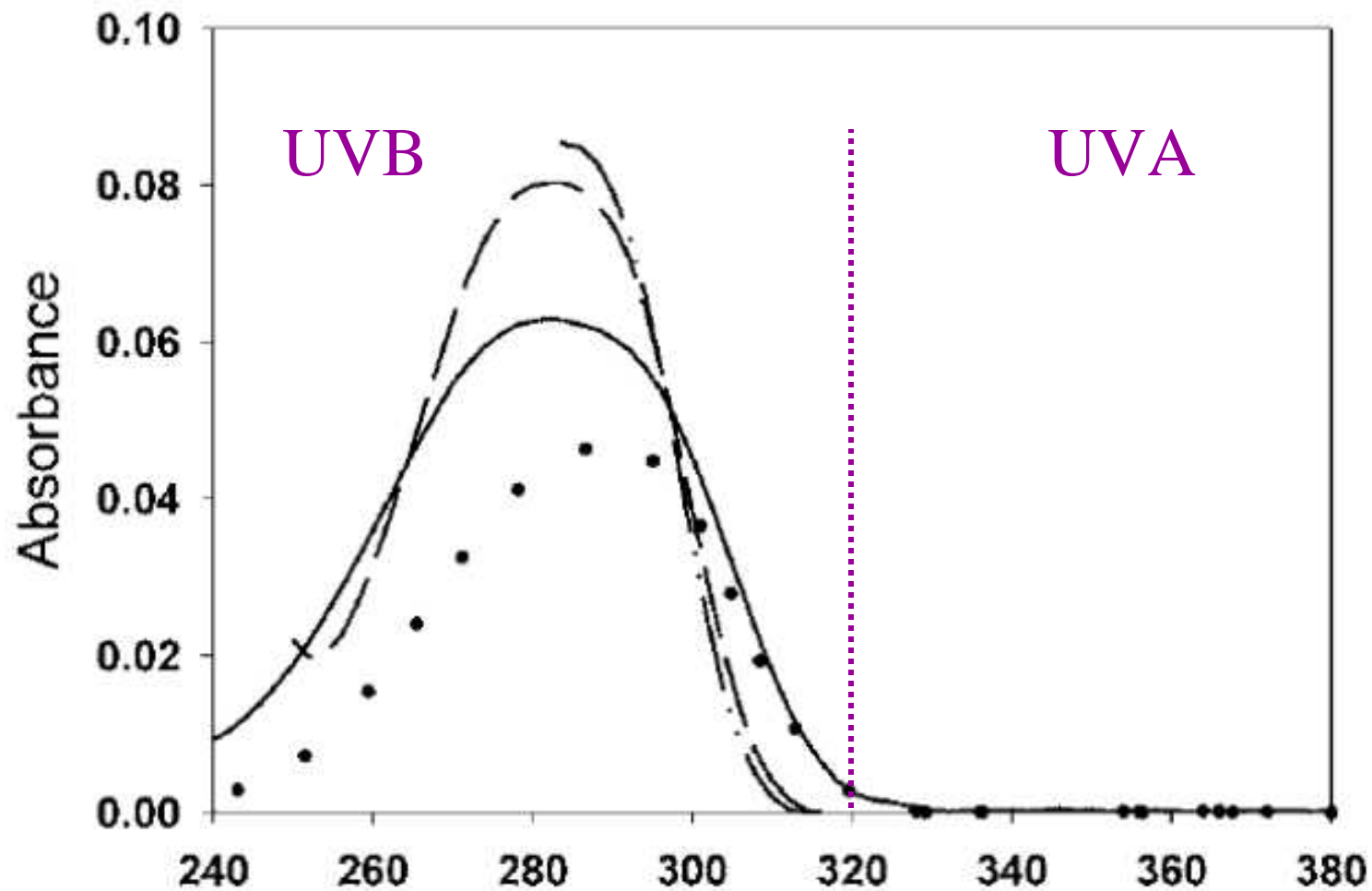
Absorption spectrum of octyl methoxycinnamate in toluene (· · ·); ethyl acetate (-.-); 1 propanol (---); and methanol (—)

Source: Krishnan R, Carr A, Blair E, Nordlund TM. Optical spectroscopy of hydrophobic sunscreen molecules adsorbed to dielectric nanospheres. Photochem Photobiol. 2004 Jun;79(6):531-9



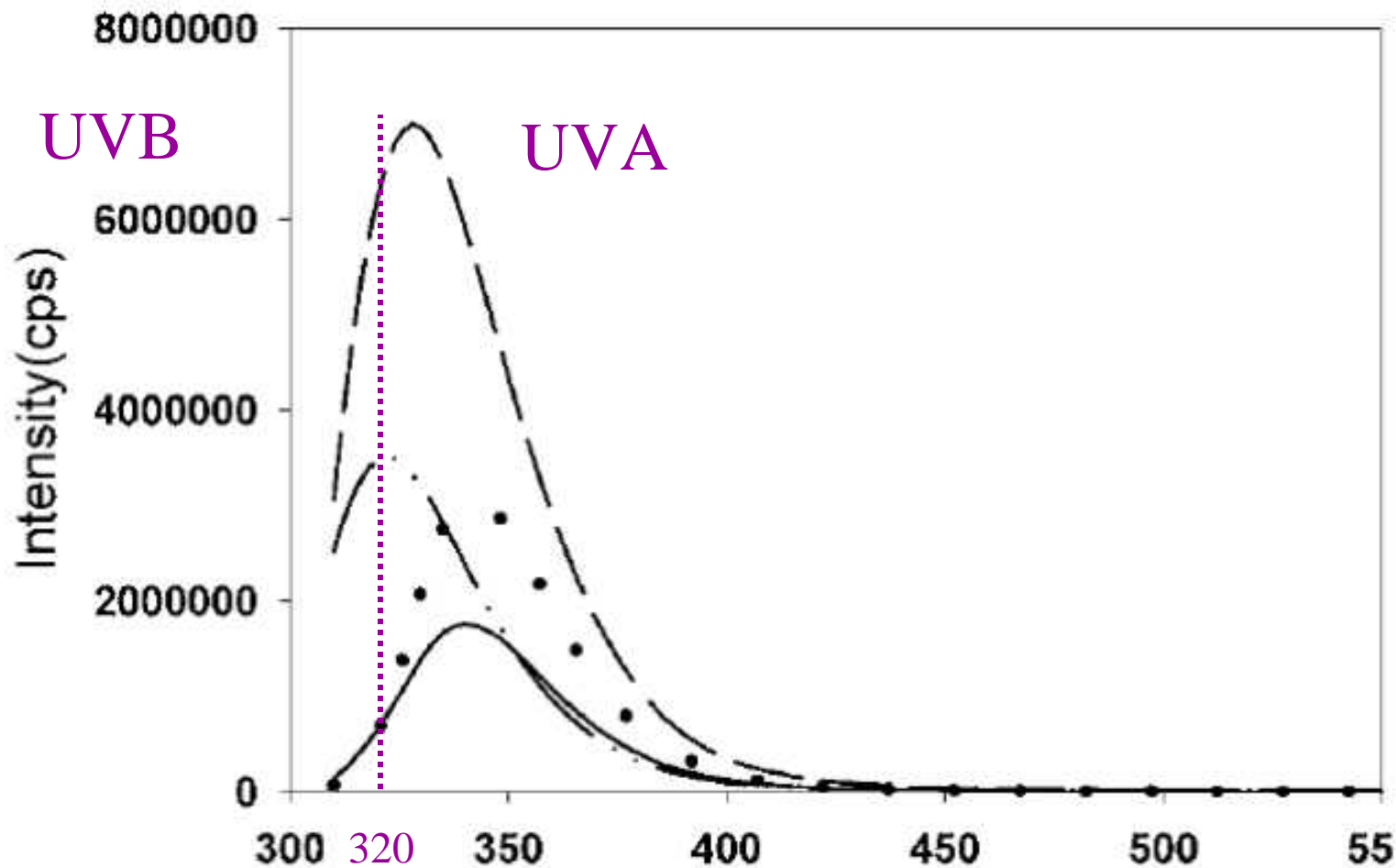
Emission spectrum of octyl methoxycinnamate
in toluene (---); ethyl acetate (-.-); 1 propanol (....); and methanol (—)

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Absorption spectrum of PABA
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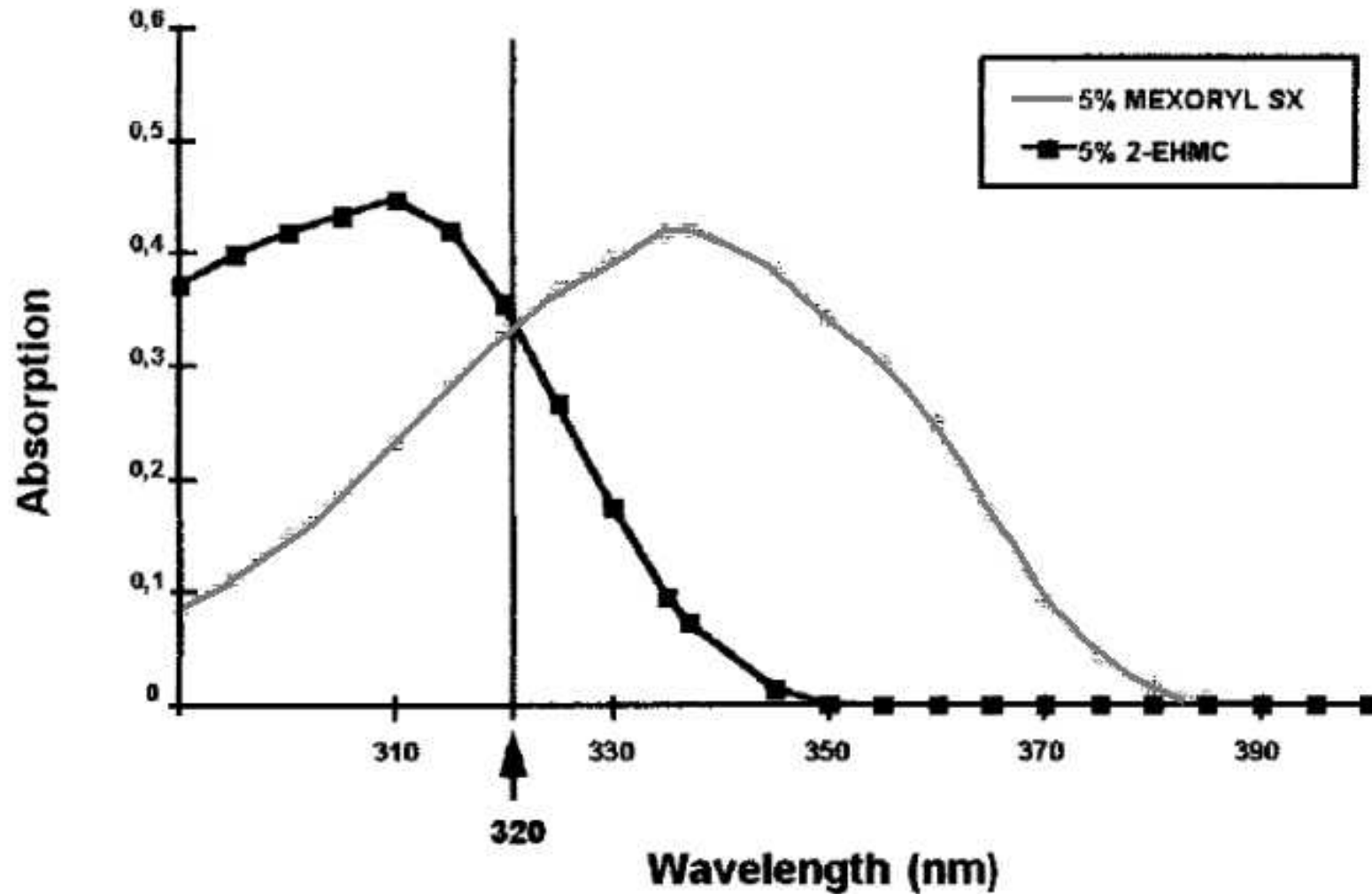
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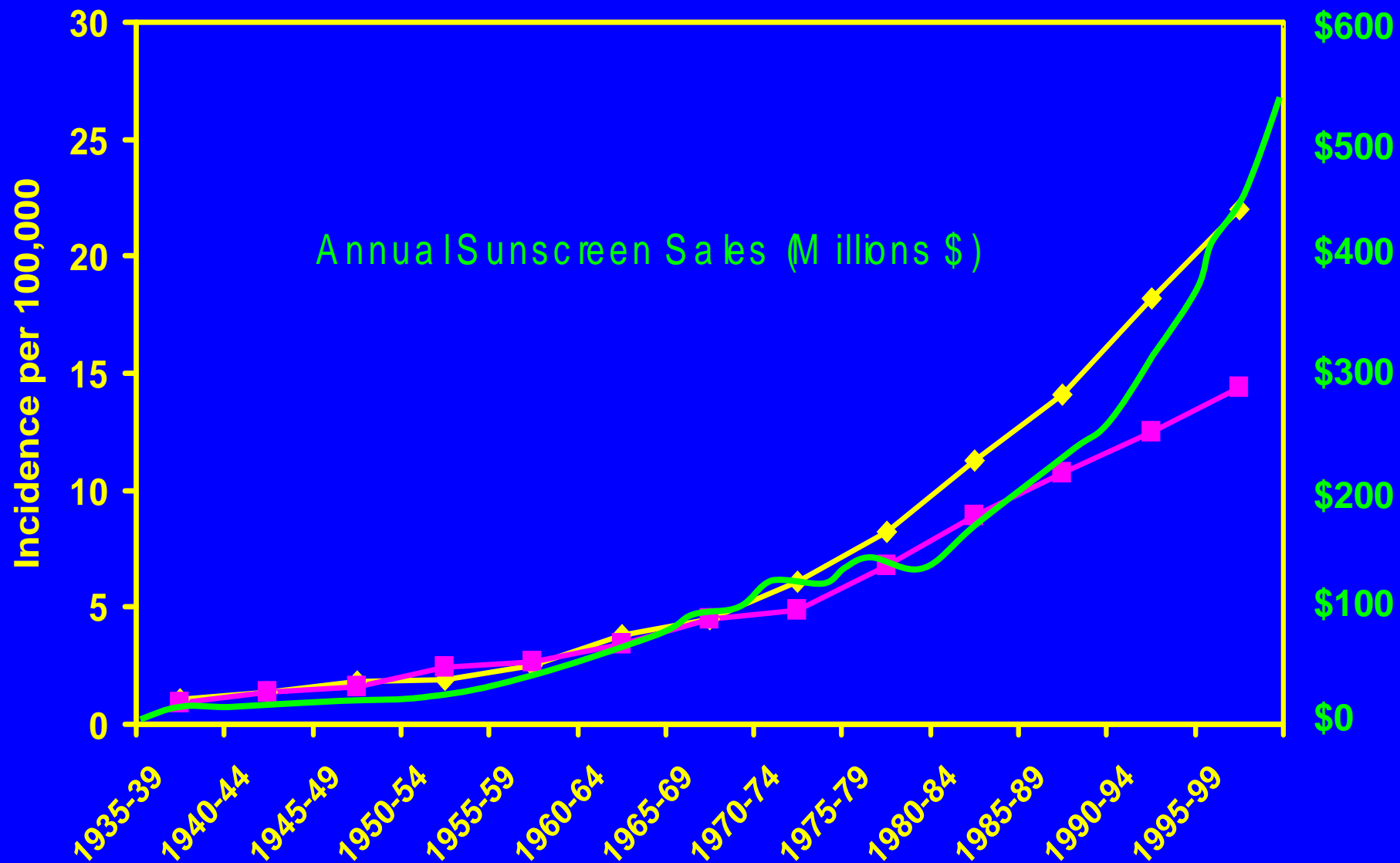
Absorption spectrum of 5 % Mexoryl SX and 5%2-EHMC

Source: Bernard F, Vioux C, Asselineau D. Evaluation of the protective effect of sunscreens on in vitro reconstructed human skin exposed to UVB or UVA irradiation. Photochem Photobiol. 2000 Mar;71(3):314-20.

Melanoma incidence in Connecticut, 1935-1999

Source: Connecticut Tumor Registry

◆ Male ■ Female



American Academy of Pediatrics



For Young Children:

Apply sunscreen at least 30 minutes before going outside, and use sunscreen even on cloudy days. The SPF should be at least 15.

Potential Recommendations for Primary Prevention of Melanoma

Should we:

- Minimize UVA exposure while allowing some UVB exposure
- If skin type allows, advise 10-15 minutes per day in the sun between 10:00 AM and 2:00 PM. Expose \geq 40% of skin area
- In AUS , NZ, and N Europe maintain vitamin D adequacy by supplementation (1,000-2,000 IU per day, NAS No adverse effect level, 1997)
- Use only sunscreens that attenuate the entire UVA spectrum by 10-20X (probably only mixtures with TiO₂)
- Do not expect that clear sunscreens will prevent melanoma- advise hats and clothing
- Replace the erythemal SPF with a ultraviolet protection factor (UPF) that includes UVA

Gauging your Vitamin D Status

What is the best serum 25 (OH) Vitamin D concentration?

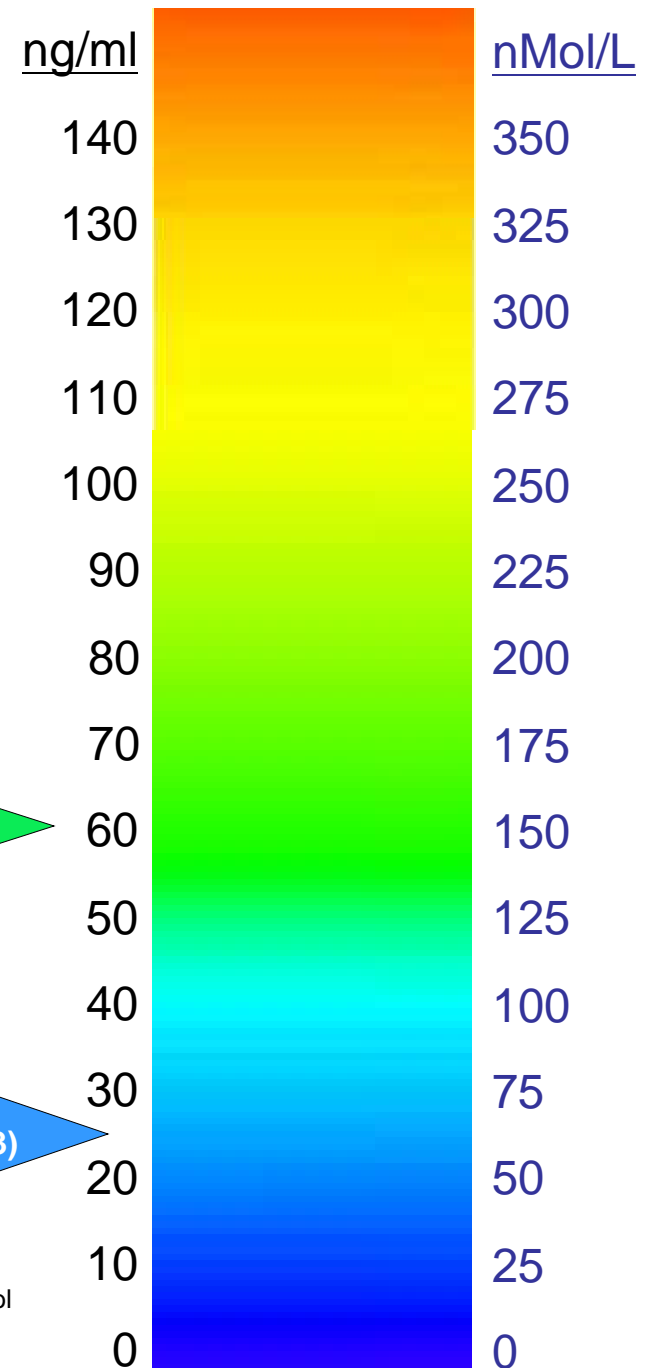
People living in sunny places with minimal clothing that doesn't limit vitamin D photosynthesis have serum 25(OH)D levels of 54 to 90 ng/ml (1).

A good target is:

60 ng/ml good target

A useful rule of thumb is that for every 100 IU of vitamin D₃ ingested, you'll gain 1 ng/mL in serum 25 (OH)D; so if your current level is 40 ng/ml you should take 2,000 IU to get up to 60 ng/ml (2).

25 ng/ml US median (NHANES 3)



1. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr. 2005;135:317-22

2. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr. 2003;77:204-10.



“W e ll, Dona ld – forgot your sun b bck, I see .”

