Sunce, vitamin D i koža

Lidija Kandolf Sekulović
Klinika za kožne i polne bolesti VMA

Vitamin D u fokusu

Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity

John S Adams and Martin Hewison*

NATURE CLINICAL PRACTICE ENDOCRINOLOGY & METABOLISM FEBRUARY 2008 VOL 4 NO 2

Vitamin D signalling pathways in cancer: potential for anticancer therapeutics

Kristin K. Deeb, Donald L. Trump‡ and Candace S. Johnson**

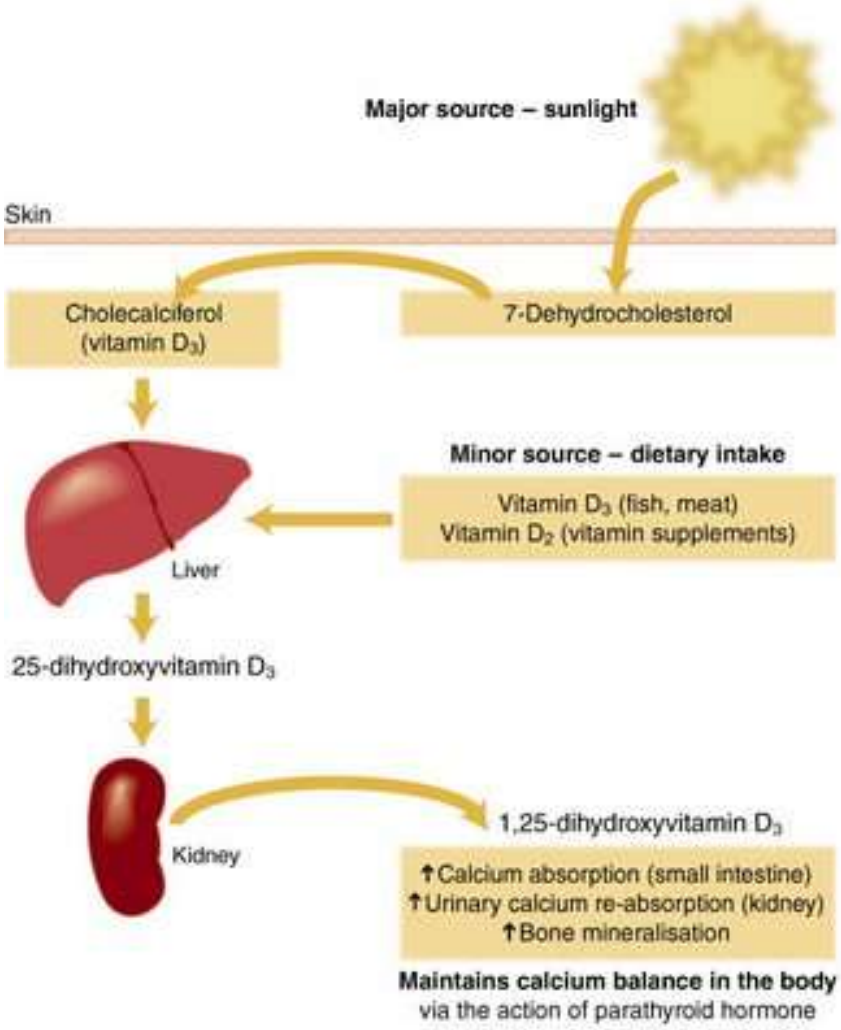
NATURE REVIEWS | CANCER VOLUME 7 | SEPTEMBER 2007

Vitamin D as a potential modifier of diabetes risk

Seenia V Peechakara and Anastassios G Pittas*

NATURE CLINICAL PRACTICE ENDOCRINOLOGY & METABOLISM ADVANCE ONLINE PUBLICATION

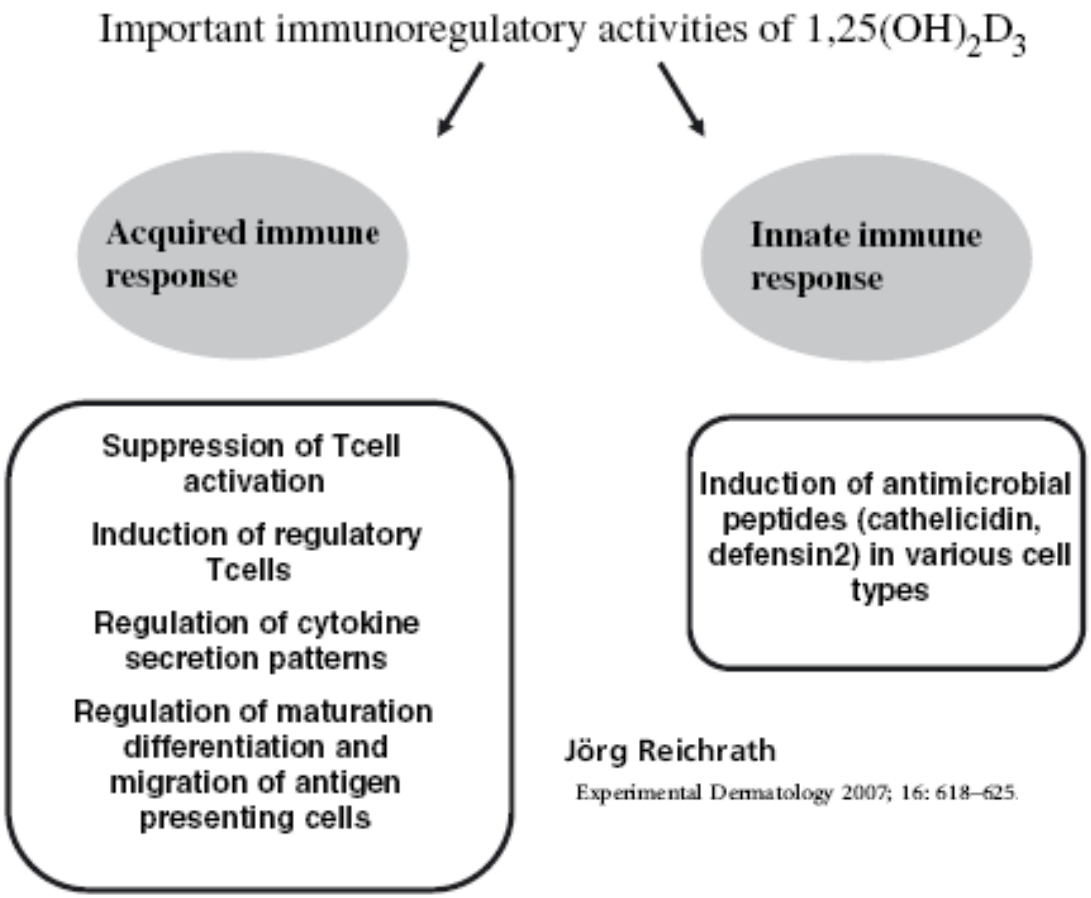
Metabolizam vitamina D



Nove uloge vitamina D

- Vitamin D i kancer
- Vitamin D i autoimunske bolesti
- Vitamin D i kardiovaskularne bolesti
- Uloga u urođenoj i adaptivnoj imunosti

Nove uloge vitamina D
imunoregulacija



Jörg Reichrath

Experimental Dermatology 2007; 16: 618–625.

Proc Natl Acad Sci U S A 2006; **103**: 11736–11741.

Nove uloge vitamina D *autoimunska oboljenja?*

- **Multipla skleroza**
  - Manje koncentracije vitamina D (deficijencija) povezane sa većim rizikom za detekciju novih lezija na MR i nesignifikantno većim rizikom za relaps Ann Neurol 2012, Aug
  - SOLAR studija – suplementacija vitaminom D uz interferon beta kod MS – randomizovana kontrolisana studija, 2011.

Nove uloge vitamina D *autoimunska oboljenja?*

- **Diabetes mellitus tip I**
  - Suplementacija dece do 1. godine smanjuje rizik od diabetes mellitusa tip I

  - **CaDDM studija**: Am J Clin Nutr 2011

    suplementacija holekalciferol vs kalcijum kod osoba sa rizikom za DM - poboljšanje oGTT testa značajno, HbA1c manje raste ali bez statističke značajnosti

Nove uloge vitamina D *autoimunska oboljenja?*

- **Reumatoidni artritis:** J Rheumatol 2011 Jan
  - Deficijencija vitamina D češća povezana sa većim skorovima aktivnosti i prisustvom anti CCP At; insuficijencija vitamina D bez značaja na aktivnost RA

  - ***Women Initiative CaD trial:*** Rheumatol Int 2011 Dec

    36200 žena bez RA praćenih tokom 5 godina, pojava 163 slučaja RA

    Vitamin D vs. placebo, bez razlike u incidenci RA

    Veća izloženost vitaminu D (suplementacija+izlaganje suncu): povećan rizik za RA**!**

Nove uloge vitamina D *kardiovaskularna oboljenja?*

- Suplementacija vitaminom D kod osoba sa hipertenzijom i insuficijencijom vitamina D smanjuje vrednosti krvnog pritiska (Am J Hypertension 2012 Aug)

- Nema korelacije između statusa vitamina D i pojave kardiovaskularnih događaja kod osoba sa stabilnom anginom pectoris (Am Heart J 2012; Sep 164 (3)

- Suplementacija vitamina D kod žena u postemnopauzi nije smanjila rizik za kardiovaskularne bolesti (PloS One 2012; May)

Rizici od hipervitaminoze D:

hipekalcemija, hiperfosfatemija, povećanje koncentracije FGF

Nove uloge vitamina D *prevencija i lečenje kancera?*

- Apperly, 1941, SAD:
  - Sever vs. Jug: veći rizik za kancer unutrašnjih organa, manji za kancer kože i obrnuto
- Garland et al. rizik od razvoja karcinoma kolona i dojke povećani u severnim regionima SAD
- Hanchette et al. rizik od razvoja karcinoma prostate povećani u severnim regionima SAD

Nove uloge vitamina D *prevencija i lečenje kancera?*

- **Karcinom kolona**: randomizovana, kontrolisana studija suplementacije vitamina D tokom 7 godina žena u postmenopauzi – bez efekta na incidencu

- **Karcinom dojke**: French E3 kohort Cancer Epidemiol Biomarkers Prev; 2011

  67721 žena praćeno 10 godina

  2871 obolelih žena

  vitamin D suplementacija bez efekta na rizik

  U regijama sa najvećom UV insolacijom, vitamin D suplementi i dijeta povezani sa manjim rizikom u odnosu na žene sa najnižim unosom vitamina D

Nedostaci studija

- Nepostojanje adekvatnih kontrola
- Udruženi faktori (socioekeonomski status, zagađenje, razlike u ishrani, …)
- Problemi u metodologiji – često retrospektivne studije
- Retke randomizovane kontrolisane studije nisu potvrdile nalaze prethodnih

Vitamin D i kancer

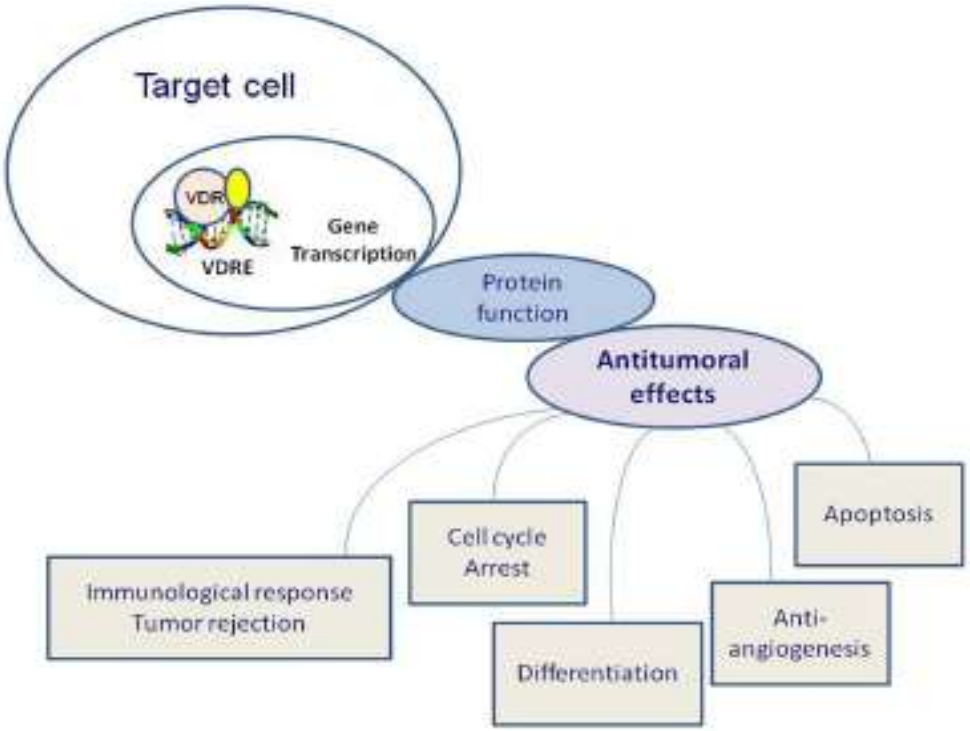


FIGURE 2 | Effects of vitamin D receptor (VDR) activation on tumorigenesis. Calcitriol bound to VDR forms heterodimers with the retinoid X receptor (RXR) and its ligand (9 *cis*-retinoic acid), these dimers occupy specific nucleotide sequences: vitamin D response elements (VDREs). In conjunction with several transcription factors, this complex lead to the transcription of vitamin D responsive genes.

Polimorfizam VDR i kancer

Table 1 | VDR polymorphisms associated with cancer.

Cancer	VDR polymorphisms
Prostate	*Fok*I, *Bsm*I, Taq, *Apa*I, poly (A)
Breast	*Fok*I, *Bsm*I, *Taq*I, *Apa*I, poly (A)
Melanoma	*Fok*I, *Bsm*I
Colorectal	*Fok*I, *Bsm*I
Thyroid	*Apa*I, *Fok*I, *Taq*I

Polimorfizam VDR i melanom

Gen/SNP	Genotip	Melanom			Kontrole		Adjusted OR* (95% CI)	p
		N	%		N	%		
VDR EcoRV	ee	15	19.74		30	32.97	1	Ref.
	Ee	47	61.84		35	38.46	**2.527** (1.145-5.575)	**0.022**
	EE	14	18.42		26	28.57	1.333 (0.471-3.767)	0.588
VDR FokI	ff	11	14.47		36	39.56	1	Ref.
	Ff	36	47.37		46	50.55	**2.499** (1.085-5.757)	**0.031**
	FF	29	38.16		9	9.89	**10.878** (3.731-31.715)	**0.000**

Ee heterozigot, Ff heterozigot, FF mutirani homozigot

Kandolf Sekulovic L, Zeljic K, et al. EADO 2012

Polimorfizam VDR i melanom

Kliničko patološki tip	VDR EcoRV		
	ee	Ee	EE
Nodularni melanom (NM)	2	17	1
Superficijalno šireći melanom (SSM)	13	30	13

P=0.043, χ^2 test

Kandolf Sekulovic L, Zeljic K, et al. EADO 2012

Vitamin D i kancer kože

- Kalcidiol smanjuje stvaranje ciklopirimidinskih dimera (markeri DNK oštećenja pod uticajem UV) u keratinocitima

MELANOM

- Ćelije melanoma eksprimiraju VDR, produkuju vitamin D i njegovom prisustvu sporihe proliferišu
- Indukcija apoptoze ćelija melanoma in vitro

Manje koncentracije serumskog vitamina D, veća debljina melanoma po Breslowu

Table 2.

Association Between Serum Vitamin D Levels at Recruitment and Breslow Thickness in the Prospective Cohort Study

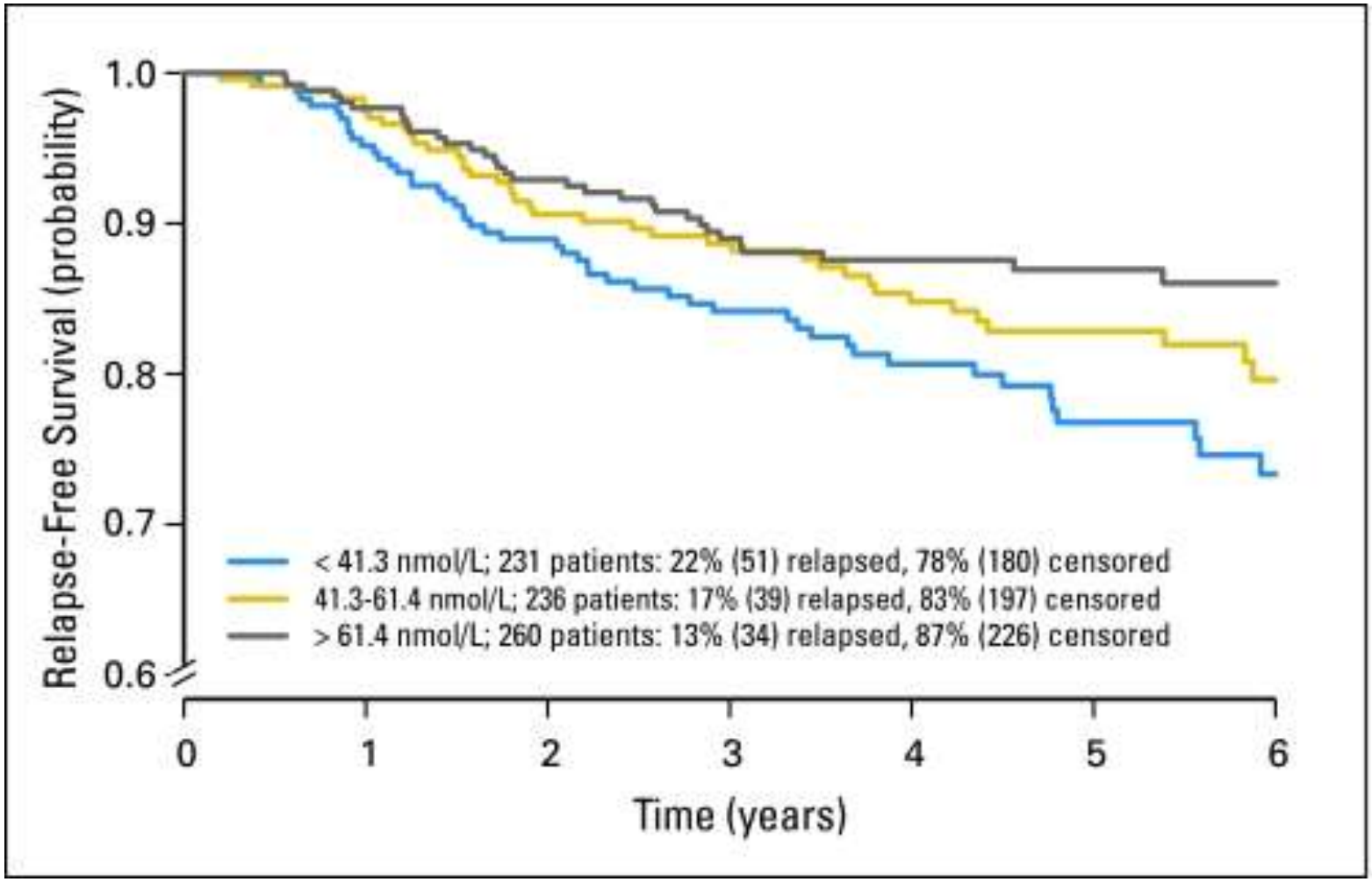
Breslow Thickness (mm)*	No. of Patients	Crude Mean	95% CI	Adjusted Mean†	95% CI
< 0.75	152	57.2	53.5 to 61.0	55.8	52.5 to 59.0
0.75-1	259	54.1	51.3 to 56.9	54.9	52.0 to 57.8
1-2	381	52.4	50.2 to 54.5	53.7	51.3 to 56.2
2-3	156	50.8	47.1 to 54.4	51.6	47.8 to 55.4
> 3	182	49.6	46.3 to 52.9	48.5	44.8 to 52.2

*Based on 1,130 melanoma cases.

†Adjusted for age, sex, body mass index, and month sampled using a general linear model. P = .002 for linear

Newton-Bishop J et al. J Clin Oncol 2009;

Veća koncentracija vitamina D, manji rizik od progresije bolesti



Efekti vitamina D u koži

- VDR u koži:
  keratinociti, sebociti, melanociti, fibroblasti
  limfociti
- Funkcije:
  - Supresija proliferacije/indukcija diferencijacije keratinocita
  - Imunomodulatorna dejstva: supresija T ćelijske aktivacije, supresija dendritičnih ćelija
  - Urođen imunost: indukcija antimikrobnih peptida u keratinocitima
  - Zaštita od oksidativnog stresa
  - Supresija UV indukovane apoptoze keratinocita

Analozi vitamina D u lečenju

- Psorijaza
- Lokalizovana sklerodermija
- Lichen sclerosus
- Vitiligo
- Akne?

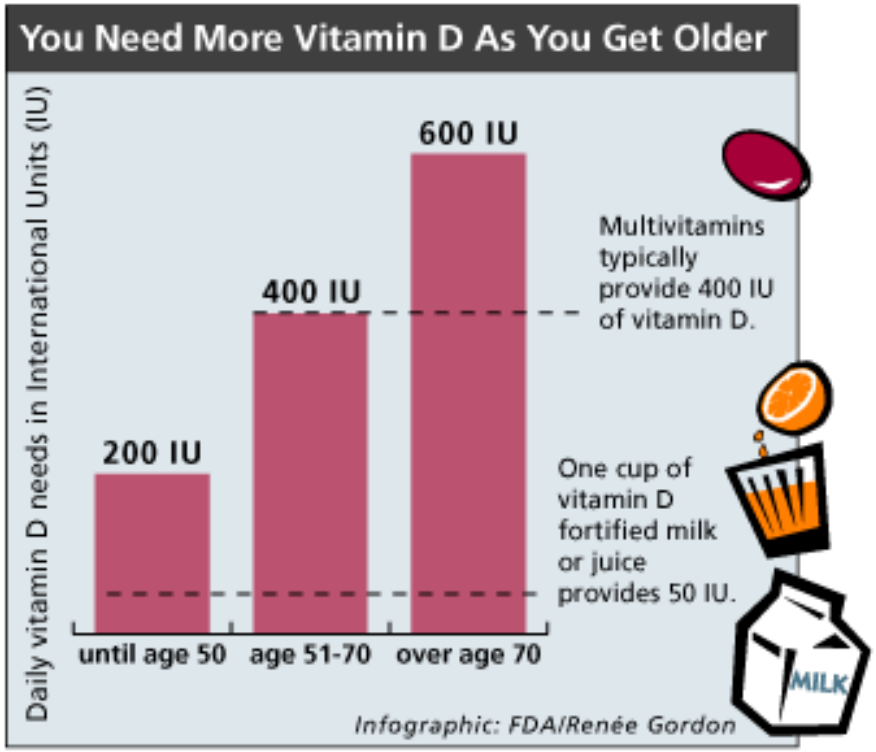
Vitamin D status

Deficijencija < 20 ng/mL

Insuficijencija 21-29 ng/mL

Suficijencija 30-100 ng/mL

Koliko je vitamina D potrebno?



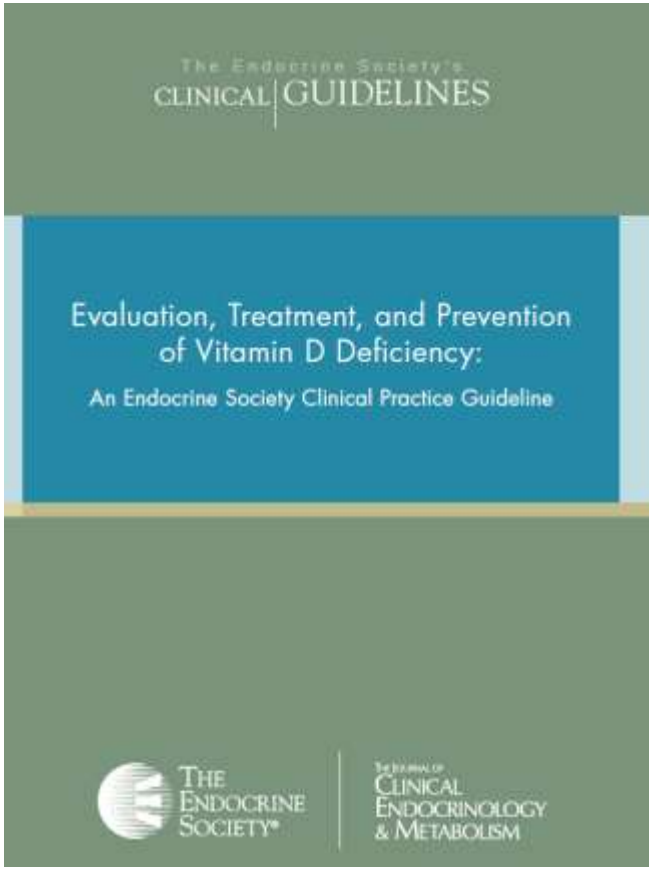
- Nove preporuke? 1000-4000 IU/d

Nove preporuke

Deca <1 godine:
400-1,000 IU/d

Deca 1-18 godina:
minimum 600, optimum1,000 IU/d

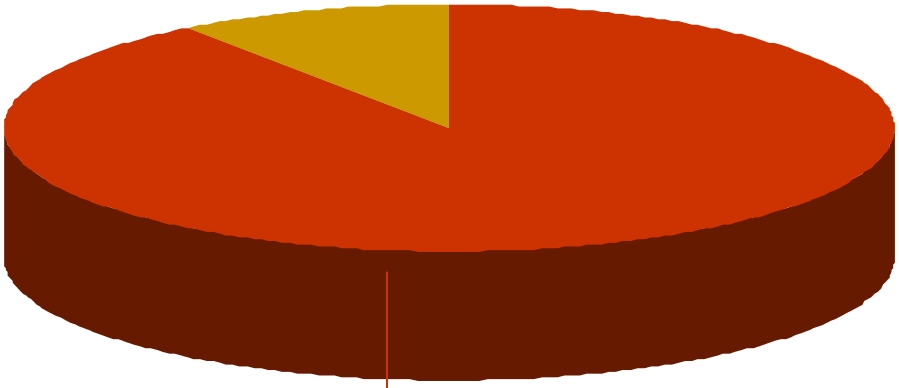
Odrasli:
minimum 600-800, optimum 1.500-2.000 IU/d



2011

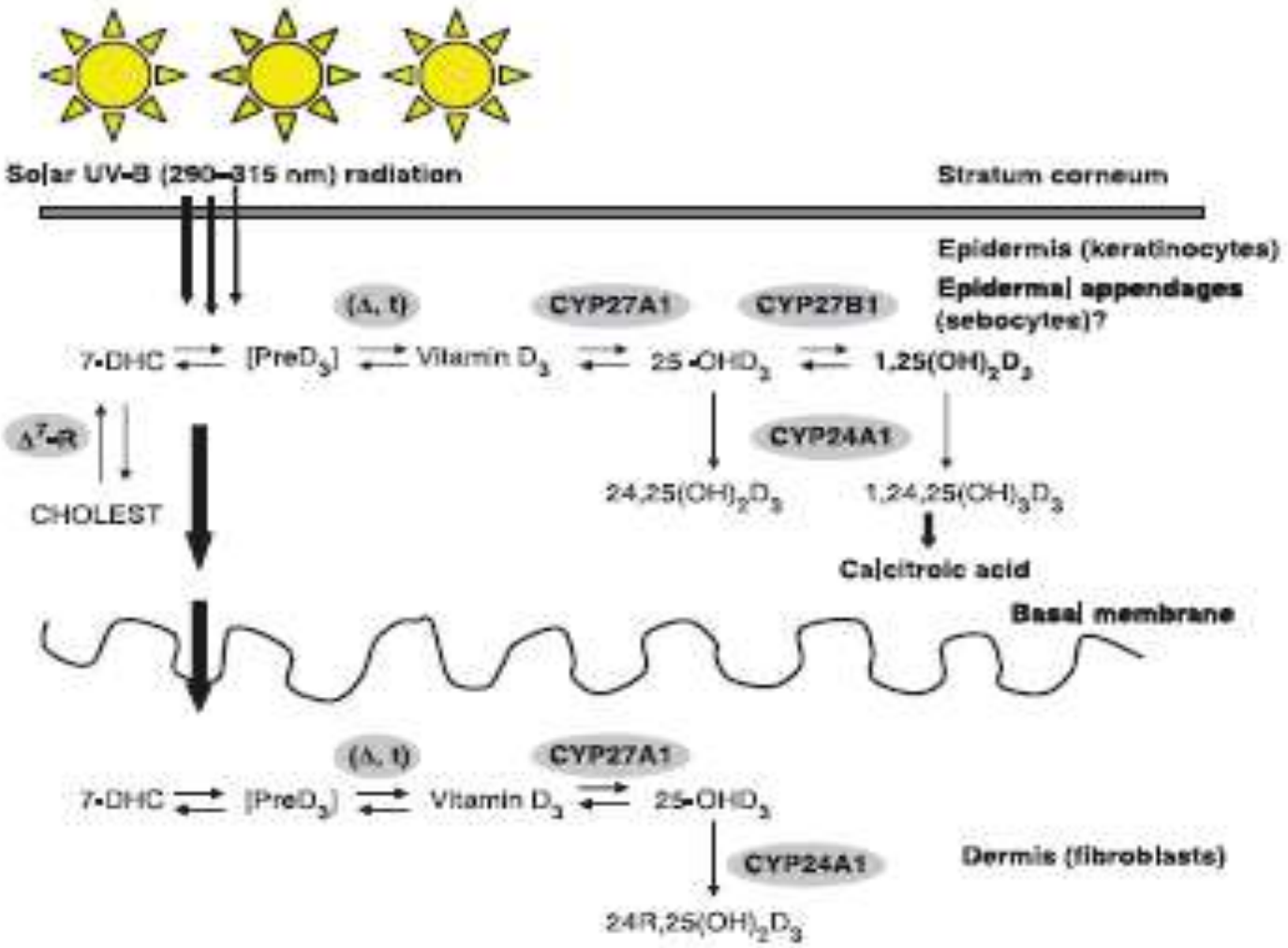
Izvori vitamina D

Hrana i suplementi 10-20%

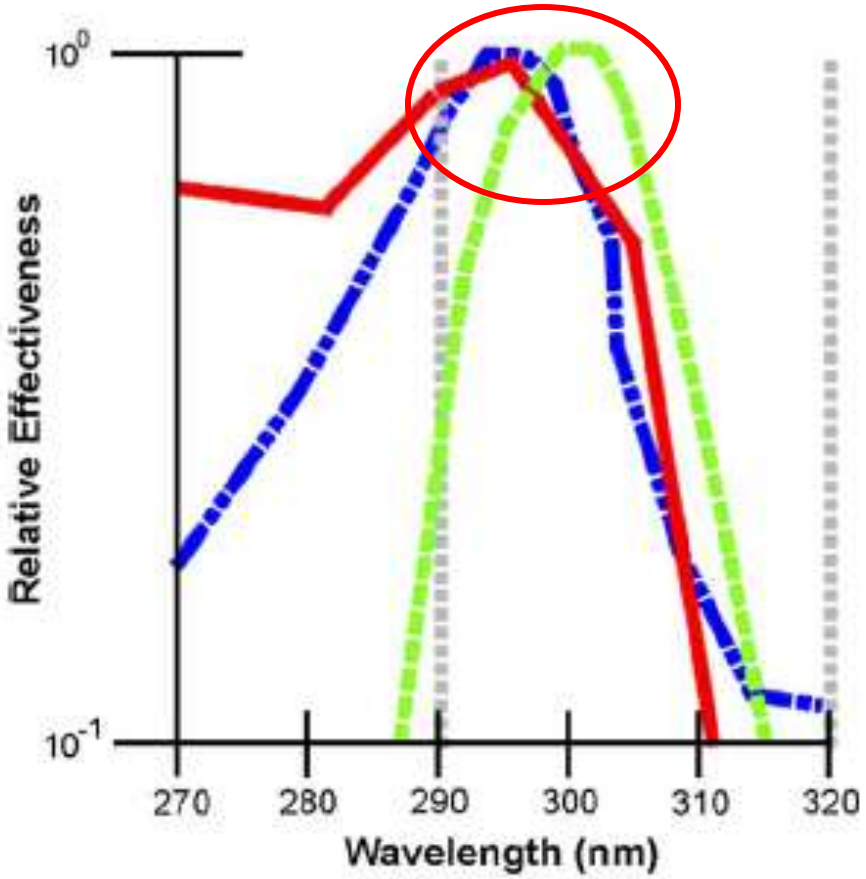


Fotosinteza u koži 80-100%

Sinteza vitamina D u koži



Akcijski spektar – UVB (290-320 nm)



sinteza vitamina D

oštećenje DNK i kancerogeneza

opekotina od sunca eritem

Sinteza vitamina D u koži

- Sinteza dostiže plato
  posle metabolisanja 10-20% 7-DHC
- Svako dalje izlaganje suncu:
  7-DHC inaktivni metaboliti
  zaštita od hipervitaminoze D!

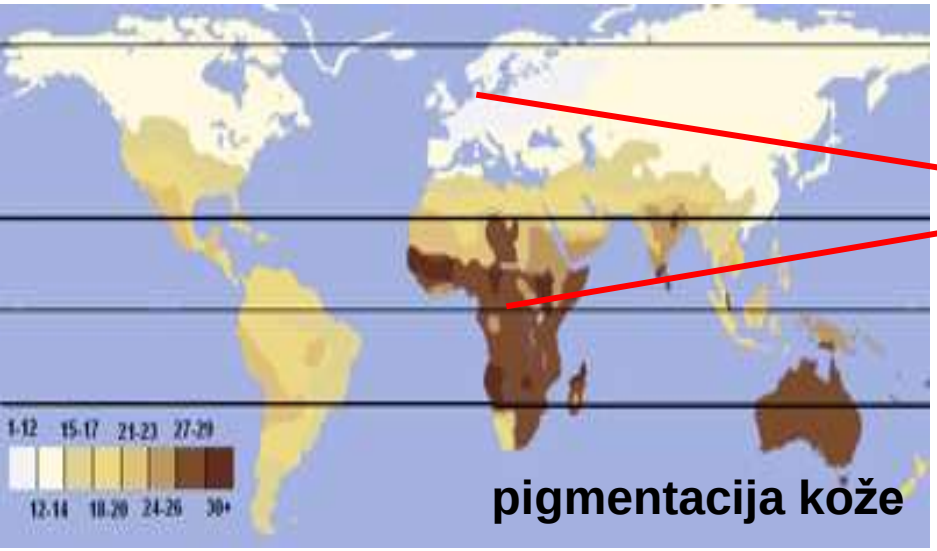
Faktori koji utiču na sintezu

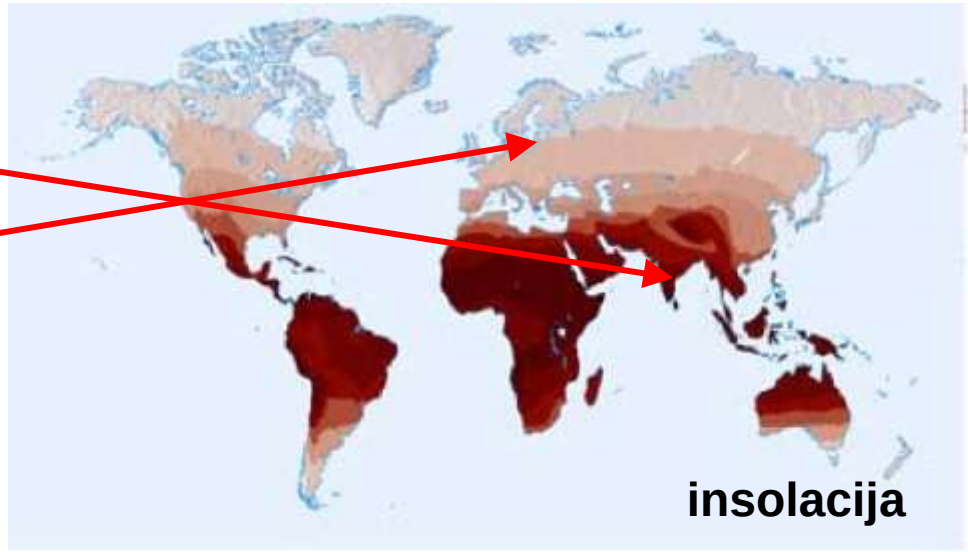
- Spoljašnji faktori - količina UV zračenja
  - geografska širina
  - doba godine
  - oblačnost: kumulusi/stratusi
  - atmosfersko zagađenje
  - nadmorska visina

- Unutrašnji faktori
  - tip kože
  - uzrast
  - odeća i SPF zaštitne kreme
  - kulturološki obrasci ponašanja

Tip kože i geografska širina

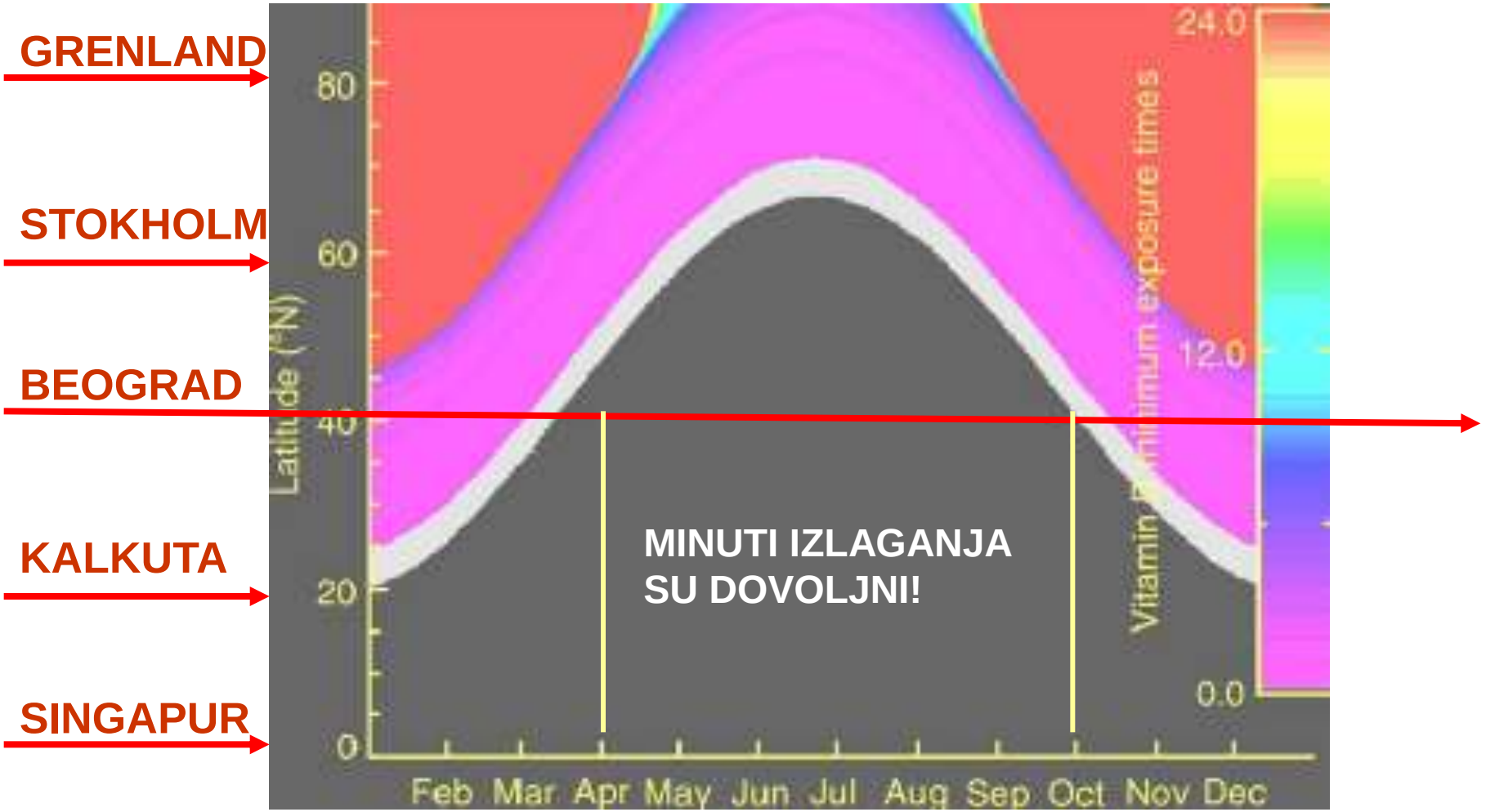
Rizik od deficijencije vit D





Rizik od kancera kože

Dovoljno sunca za 1000 IU?



Ann R. Webb* Progress in Biophysics and Molecular Biology 92 (2006) 17–25

Dovoljno sunca?

- Hollick et al. Am J Clin Nutr 2004; 79(3): 362.

koža tip II
izlaganje celog tela 5 minuta
juni u podne
Boston, SAD (43 N)

= 10 000 IU

  - 15% tela (lice, šake, ruke) = 1500 IU/d

- Marks R et al. Arch Dermatol 1995; 131: 415.
  5% površine kože <MED = 35 nmol/L 25-OH vit D

Dovoljno sunca?

Exposure times needed to achieve vitamin D concentrations of 200, 400, and 600 IU, depending on the UV index

	UV index (1 = low, 12 = high)			
	1	3	6	12
Exposure time (min) for the production of:				
200 IU vitamin D	46	15	8	4
400 IU vitamin D	93	31	16	8
600 IU vitamin D	140	47	24	12
Skin type II: minimal erythema doses per hour (MED/h)	0.42	1.26	2.52	5.04

6% kože izloženo, fototip II

Deutsches Ärzteblatt International | Dtsch Arztebl Int 2010; 107(37): 638–43

Dovoljno sunca?

Estimates of beneficial and harmful sun exposure times during the year for major Australian population centres

MJA • Volume 184 Number 7 • 3 April 2006

2 Solar ultraviolet (UV) radiation exposure period (minutes) at 12:00 to produce 1/6 to 1/3 minimal erythemal dose (MED), sufficient for vitamin D production, and 1 MED (erythema; in parentheses*), for people with type II skin and 15% of the body exposed

	Exposure period (minutes)											
City†	Jan	Feb	Mar	Apr	May	June	Jul	Aug	Sep	Oct	Nov	Dec
Townsville	2–5	3–6	2–5	3–6	3–7	5–10	4–8	3–6	3–5	2–4	2–4	2–4
	(10)	(10)	(10)	(14)	(16)	(22)	(19)	(14)	(12)	(10)	(10)	(9)
Brisbane	2–4	3–5	3–6	4–8	5–11	7–14	6–12	4–9	4–8	3–6	3–6	3–5
	(8)	(11)	(10)	(14)	(22)	(34)	(30)	(23)	(17)	(14)	(12)	(11)
Perth	2–4	2–4	3–5	4–8	7–15	9–17	9–17	6–12	5–10	3–6	2–5	2–5
	(10)	(11)	(13)	(19)	(30)	(42)	(38)	(25)	(20)	(14)	(12)	(11)
Sydney	3–6	2–5	4–8	5–9	8–16	10–19	11–22	7–14	5–9	3–7	3–7	3–6
	(11)	(11)	(14)	(20)	(30)	(48)	(40)	(30)	(19)	(16)	(12)	(11)
Adelaide	2–4	2–5	3–6	6–11	9–17	15–30	12–25	8–16	6–11	4–8	3–6	3–5
	(11)	(11)	(13)	(22)	(33)	(55)	(48)	(32)	(20)	(16)	(13)	(11)
Melbourne	3–6	2–5	4–8	6–13	11–22	17–34	17–34	11–23	7–13	5–10	4–8	3–6
	(10)	(10)	(15)	(23)	(38)	(70)	(51)	(37)	(23)	(19)	(14)	(12)
Hobart‡	7–14	7–14	11–22	18–36	28–56	37–75	55–110	26–53	16–33	10–30	9–18	7–15
	(27)	(30)	(41)	(60)	(95)	(150)	(150)	(96)	(62)	(41)	(31)	(31)

*Exposure time to produce 1 MED (erythema) based on the maximal Ultraviolet Index (UVI) reading for that month is provided in parentheses. † Data for cities other than Hobart are based on UVI readings recorded in 2001. ‡ UVI readings for Hobart were from 1991, as reliable and comparable data for 2001 were not available.

Preporuke za zaštitu od sunca

- Izbegavati boravak na suncu od 10-16 od juna do septembra
- Nositi zaštitnu odeću i naočare
- Nanositi kremu sa SPF faktorom tokom boravka napolju u rizičnim periodima
- Prilagoditi ponašanje na osnovu izveštaja o UV indeksu
- PREPORUKE NE TREBA MENJATI ZA NAJVEĆI DEO POPULACIJE!

Be Sun Smart℠:
Protect Yourself from the Sun

Sun exposure is the most preventable risk factor for all skin cancers, including melanoma. You can have fun in the sun and decrease your risk of skin cancer.

Here's how to Be Sun Smart℠:

- Generously apply a broad-spectrum water-resistant sunscreen with a Sun Protection Factor (SPF) of 30 or more to all exposed skin. Broad-spectrum provides protection from both ultraviolet A (UVA) and ultraviolet B (UVB) rays. Re-apply approximately every two hours, even on cloudy days, and after swimming or sweating.
- Wear protective clothing, such as a long-sleeved shirt, pants, a wide-brimmed hat and sunglasses, where possible.
- Seek shade when appropriate, remembering that the sun's rays are strongest between 10 a.m. and 2 p.m. If your shadow is shorter than you are, seek shade.
- Use extra caution near water, snow, and sand as they reflect the damaging rays of the sun which can increase your chance of skin cancer.
- Get vitamin D safely through a healthy diet that may include vitamin supplements. Don't seek the sun.
- Avoid tanning beds. Ultraviolet light from the sun and tanning beds can cause skin cancer and wrinkling. If you want to look like you've been in the sun, consider using a sunless self-tanning product, but continue to use sunscreen with it.
- Check your birthday suit monthly. If you notice anything changing, growing, or bleeding on your skin, see a dermatologist. Skin cancer is very treatable when caught early.

AAD 1938 AMERICAN ACADEMY OF DERMATOLOGY

SPOT SKIN CANCER

American Academy of Dermatology
1-888-462-DERM (3376)
www.aad.org

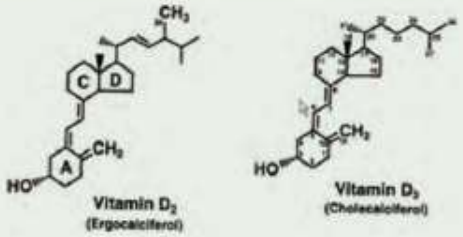
Melanom drugi malignitet po učestalosti u populaciji 15-29 godina

Rizične grupe

- Stare osobe
- Osobe sa tipom kože IV-VI
- Stanovnici urbanih sredina zimi
- Pripadnici određenih kultura
- Pacijenti sa cističnom fibrozom i sindromom kratkih creva
- Pacijenti sa povećanim rizikom za nastanak karcinoma kože:
  - transplantacija bubrega
  - xeroderma pigmentosum, Gorlinov sindrom i dr.

Preporuka za suplementaciju

TABLE 1. Sources of vitamin D_2 and vitamin D_3

SOURCE	VITAMIN D CONTENT
Natural Sources	
Cod liver oil	~400–1,000 IU/teaspoon vitamin D_3
Salmon, fresh wild caught	~600–1,000 IU/3.5 oz vitamin D_3
Salmon, fresh farmed	~100–250 IU/3.5 oz vitamin D_3, vitamin D_2
Salmon, canned	~300–600 IU/3.5 oz vitamin D_3
Sardines, canned	~300 IU/3.5 oz vitamin D_3
Mackerel, canned	~250 IU/3.5 oz vitamin D_3
Tuna, canned	236 IU/3.5 oz vitamin D_3
Shiitake mushrooms, fresh	~100 IU/3.5 oz vitamin D_2
Shiitake mushrooms, sun-dried	~1,600 IU/3.5 oz vitamin D_2
Egg yolk	~20 IU/yolk vitamin D_3 or D_2
Sunlight/UVB radiation	~20,000 IU equivalent to exposure to 1 minimal erythemal dose (MED) in a bathing suit. Thus, exposure of arms and legs to 0.5 MED is equivalent to ingesting ~3,000 IU vitamin D_3.
Fortified foods	
Fortified milk	100 IU/8 oz, usually vitamin D_3
Fortified orange juice	100 IU/8 oz vitamin D_3
Infant formulas	100 IU/8 oz vitamin D_3
Fortified yogurts	100 IU/8 oz, usually vitamin D_3
Fortified butter	56 IU/3.5 oz, usually vitamin D_3
Fortified margarine	429 IU/3.5 oz, usually vitamin D_3
Fortified cheeses	100 IU/3 oz, usually vitamin D_3
Fortified breakfast cereals	~100 IU/serving, usually vitamin D_3
Pharmaceutical sources in the United States	
Vitamin D_2 (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D_2) liquid	8,000 IU/cc
Supplemental sources	
Multivitamin	400, 500, 1,000 IU vitamin D_3 or vitamin D_2
Vitamin D_3	400, 800, 1,000, 2,000, 5,000, 10,000, and 50,000 IU

IU = 25 ng. Reproduced with permission from M. F. Holick: N Engl J Med 357:266–281, 2007 (3).

UMERENOST

(gr. *εγκρατεια*, *lat. continentia)*