Vitamin D ?

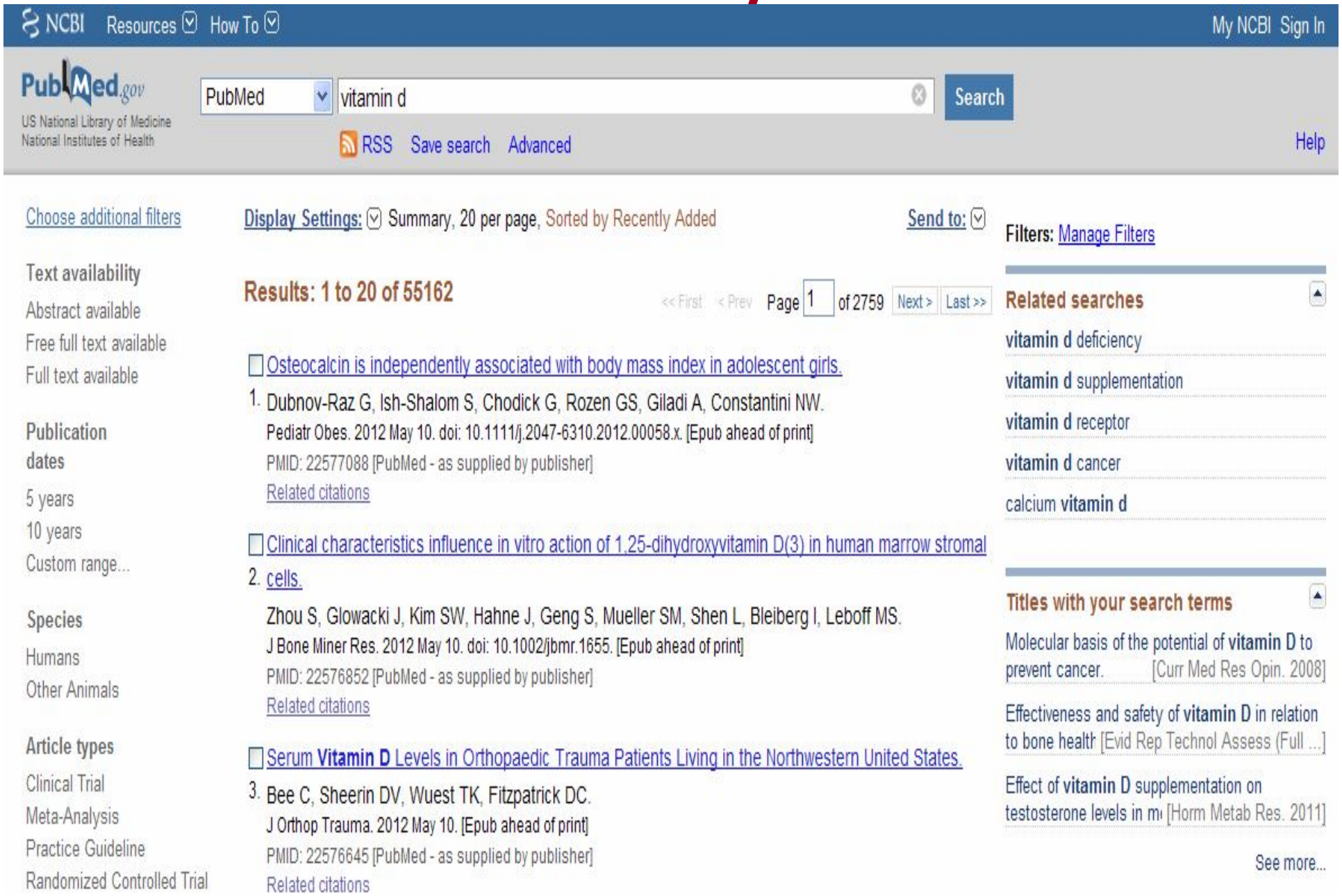
Dr. Ali Ünlü

Türk Biyokimya Derneği
16 Mayıs 2012, Ankara

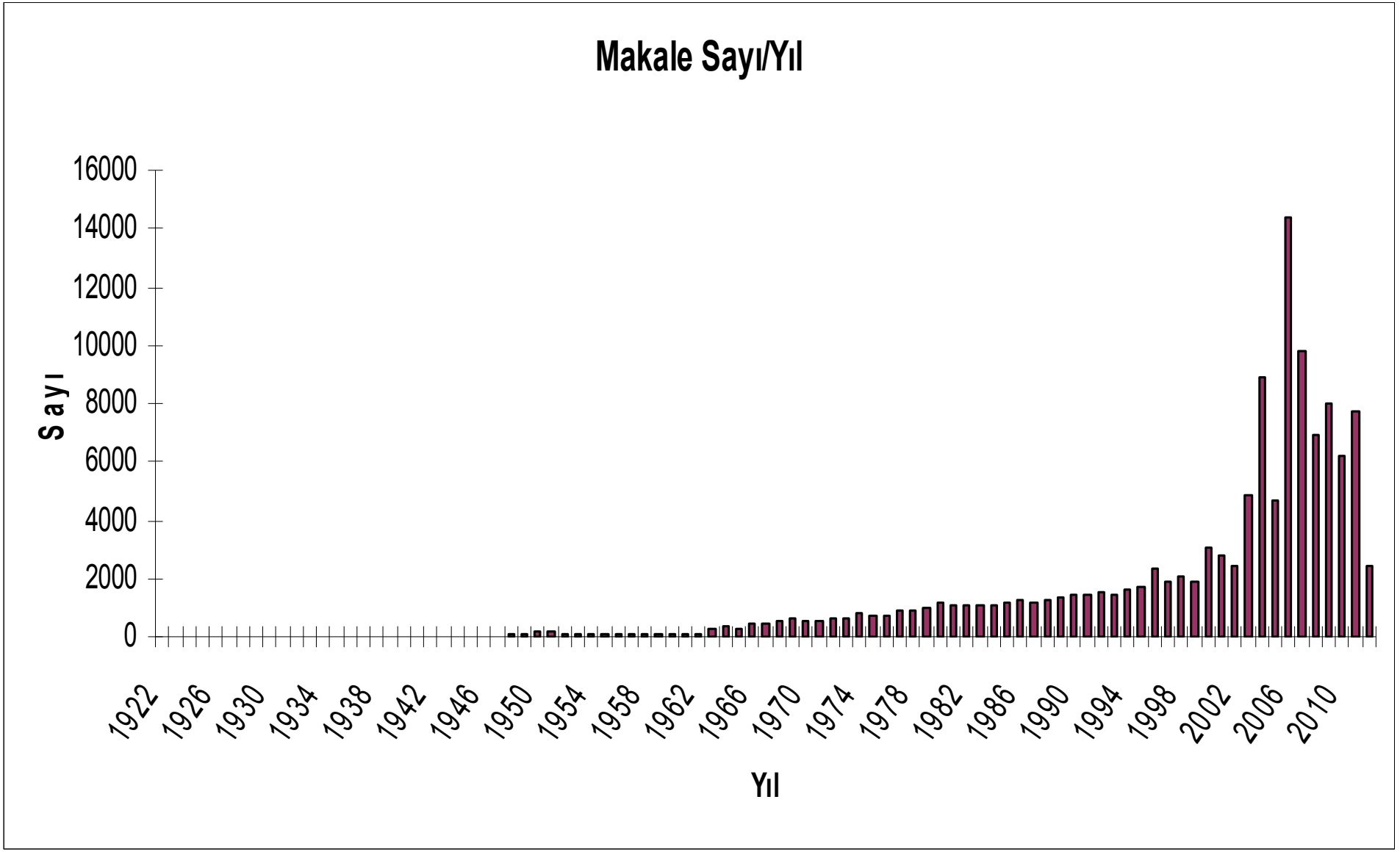
Sunum Planı

- Vitamin D tarihçe
- Besin takviye ile ilgili çalışmalar
- D Vitamini ile ilgili laboratuar çalışmaları
- D Vitamini ile ilgili epidemiyolojik çalışmalar

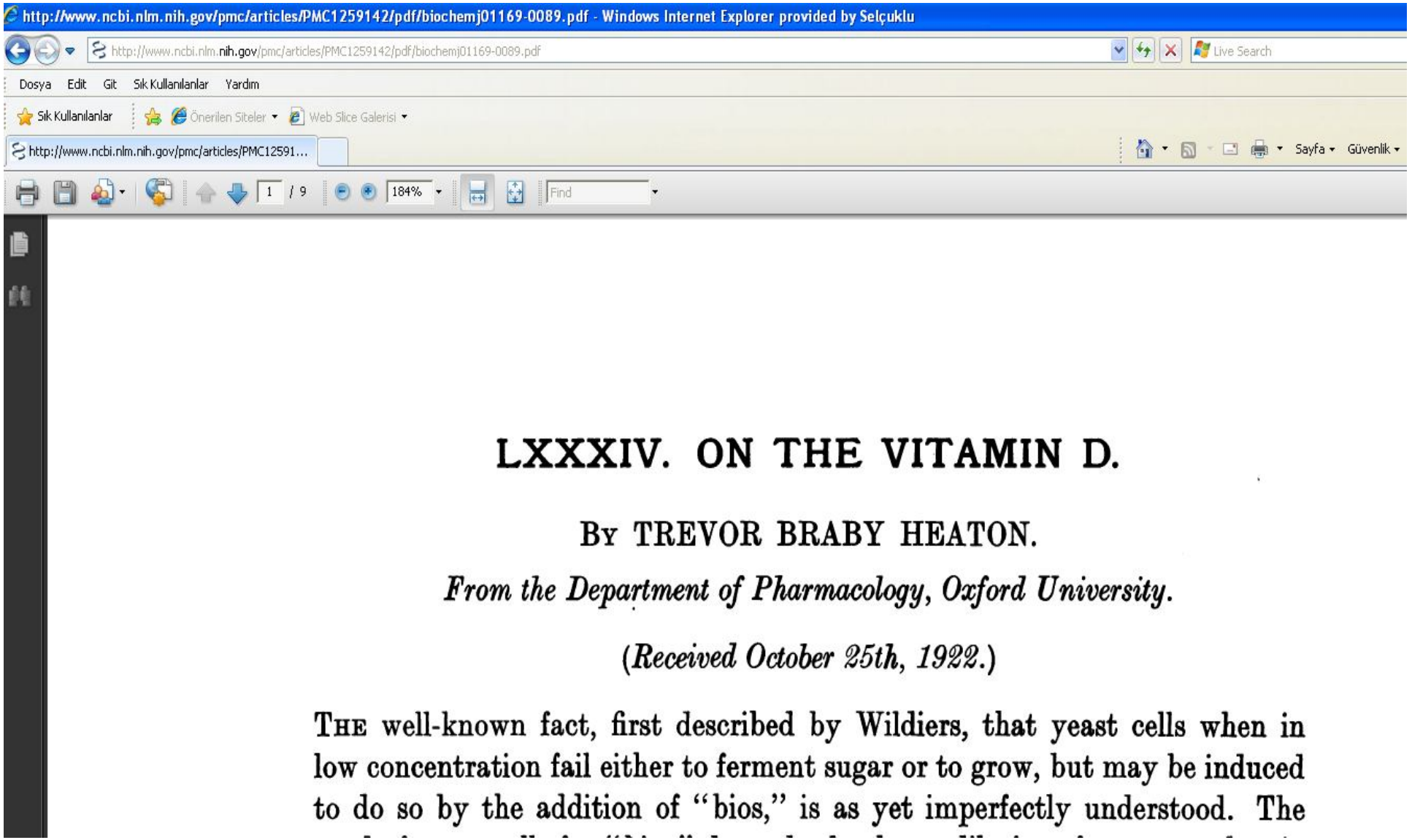
PubMed Mayıs 2012



PubMed Vitamin D Kayıtları



PubMed 1922, Bioch J



LXXXIV. ON THE VITAMIN D.

By TREVOR BRABY HEATON.

From the Department of Pharmacology, Oxford University.

(*Received October 25th, 1922.*)

The well-known fact, first described by Wildiers, that yeast cells when in low concentration fail either to ferment sugar or to grow, but may be induced to do so by the addition of "bios," is as yet imperfectly understood. The

Vitamin D Tarihsel Süreç

- İlk yayın 1645, Daniel Whistler; Rikets (Medikal Doktora Tezi), Hollanda
- 1650 Francis Glisson, De Rachitide.
- 20. yüzyıla kadar önemli bir gelişme yok. 20. yüzyılda şehirlere artan göç, ağır endüstri kullanımı ile artan hava kirliliği, güneş yüzü göremeyen şehirler nedeni ile raşitizm olgularında epidemik artış.
- Deneysel raşitik hayvan modellerin gelişimi, radyolojik görüntüleme, balık yağı ve UV ışın ile tedavi yöntemlerinin gelişmesi

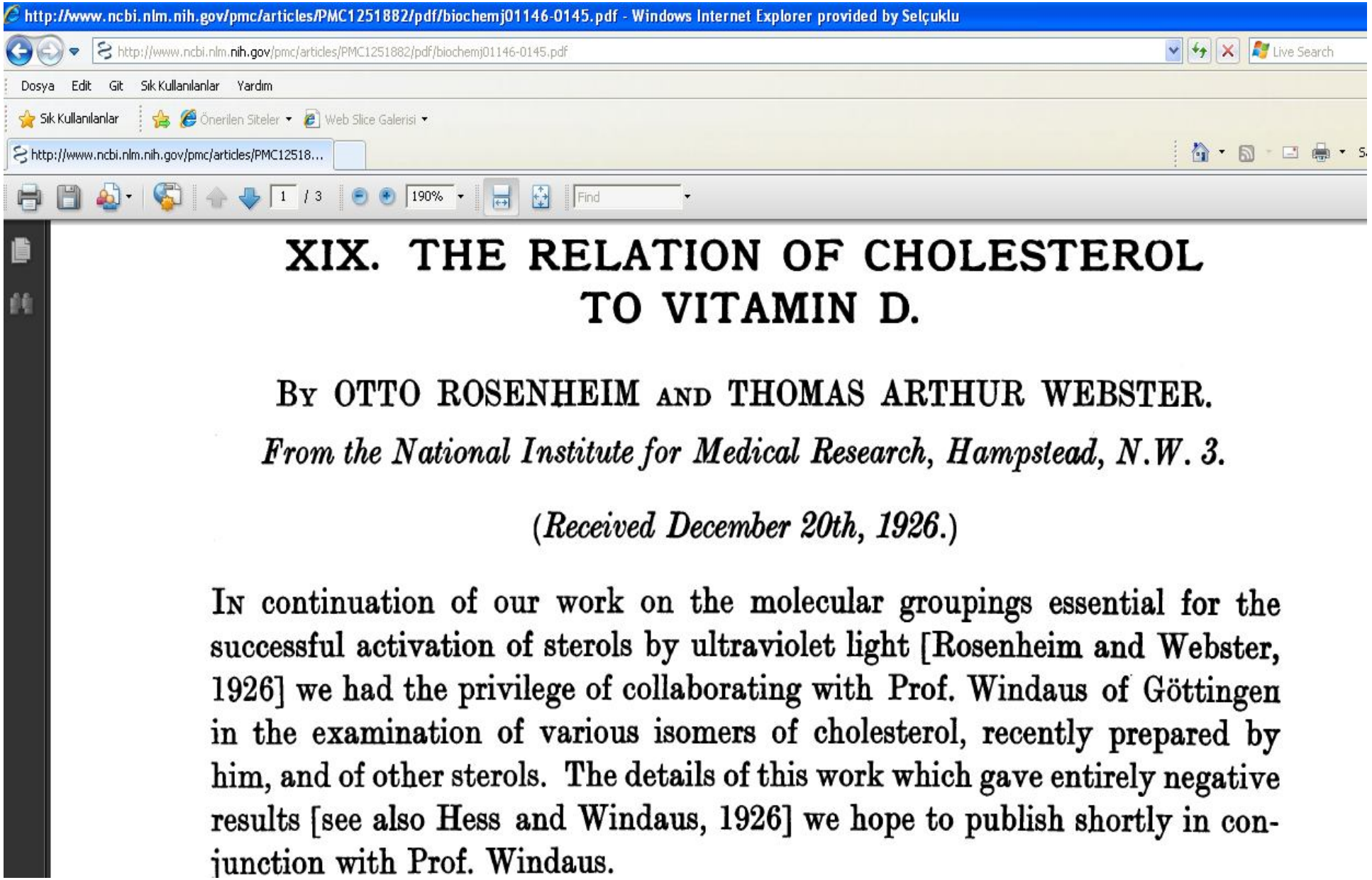
Vitamin A-D

- Balık yağı ile raşitizmin tedavisi nedeni ile ilk olarak yağda eriyen A molekülü sonrada vitamin A olarak tanımlanmış. Balık yağının ısıtılması ile Vitamin A fonksiyonlarının kaybolmasına rağmen anti-raşitik etkilerinin devam etmesi ile Vitamin D olarak adlandırılıyor (McCollum 1922).

Vitamin D-Güneş Işığı

- 1822, Varşova merkezde (hava kirliliği çok fazla) raşitizm oranı kenar semtlere göre daha fazla (Jedrzej Sniadecki)
- 1890, Theobald Palm enlem ile raşitizm sıklığında ters orantı.
- 1916, Auguste Rollier, fototerapi ile raşitizm olgularında iyileşme
- 1936, Hess 334 nm'den düşük dalga boylu ışığın filtre edildiğinde raşitizm tedavisinde faydalı olmadığını göstermiş.
- 290-310 nm UV.
- UV ışın toplam solar radyasyonun %1'den az ve yeryüzüne ulaşabilen en kısa güneş ışın dalga boyu 290 nm.
- Tbc vakalarına bol miktarda balık yağı.
- %80 D vitamin kaynağımız deri.

Kolesterol-Vit D 1926, Bioch J



XIX. THE RELATION OF CHOLESTEROL TO VITAMIN D.

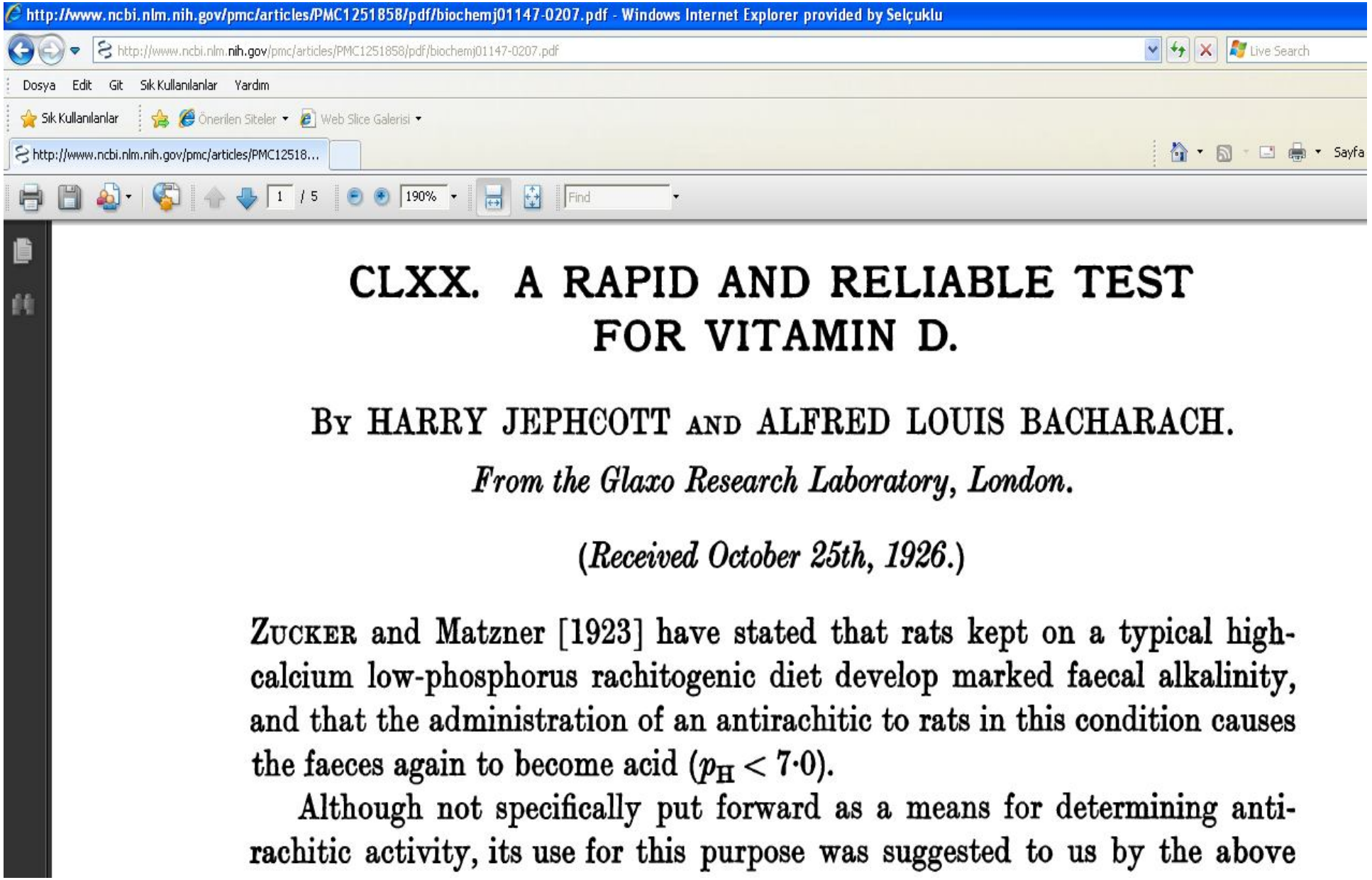
BY OTTO ROSENHEIM AND THOMAS ARTHUR WEBSTER.

From the National Institute for Medical Research, Hampstead, N.W. 3.

(*Received December 20th, 1926.*)

IN continuation of our work on the molecular groupings essential for the successful activation of sterols by ultraviolet light [Rosenheim and Webster, 1926] we had the privilege of collaborating with Prof. Windaus of Göttingen in the examination of various isomers of cholesterol, recently prepared by him, and of other sterols. The details of this work which gave entirely negative results [see also Hess and Windaus, 1926] we hope to publish shortly in conjunction with Prof. Windaus.

Vit D Analizi, 1926 Bioch J



CLXX. A RAPID AND RELIABLE TEST FOR VITAMIN D.

By HARRY JEPHCOTT and ALFRED LOUIS BACHARACH.

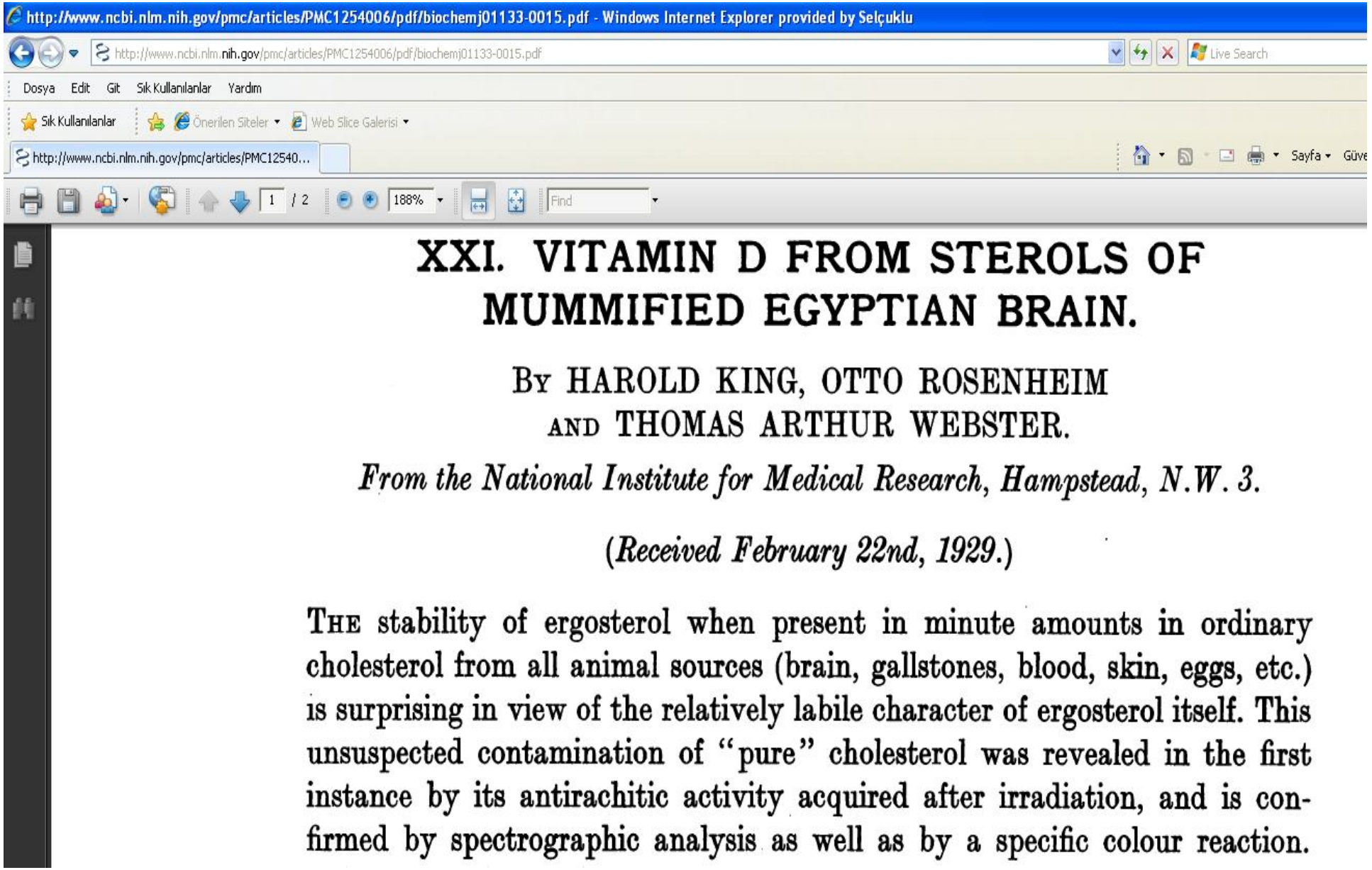
From the Glaxo Research Laboratory, London.

(*Received October 25th, 1926.*)

Zucker and Matzner [1923] have stated that rats kept on a typical high-calcium low-phosphorus rachitogenic diet develop marked faecal alkalinity, and that the administration of an antirachitic to rats in this condition causes the faeces again to become acid ($p_H < 7{\cdot}0$).

Although not specifically put forward as a means for determining anti-rachitic activity, its use for this purpose was suggested to us by the above

Mumya beyin ekstraktları raşitizm önlüyor



XXI. VITAMIN D FROM STEROLS OF MUMMIFIED EGYPTIAN BRAIN.

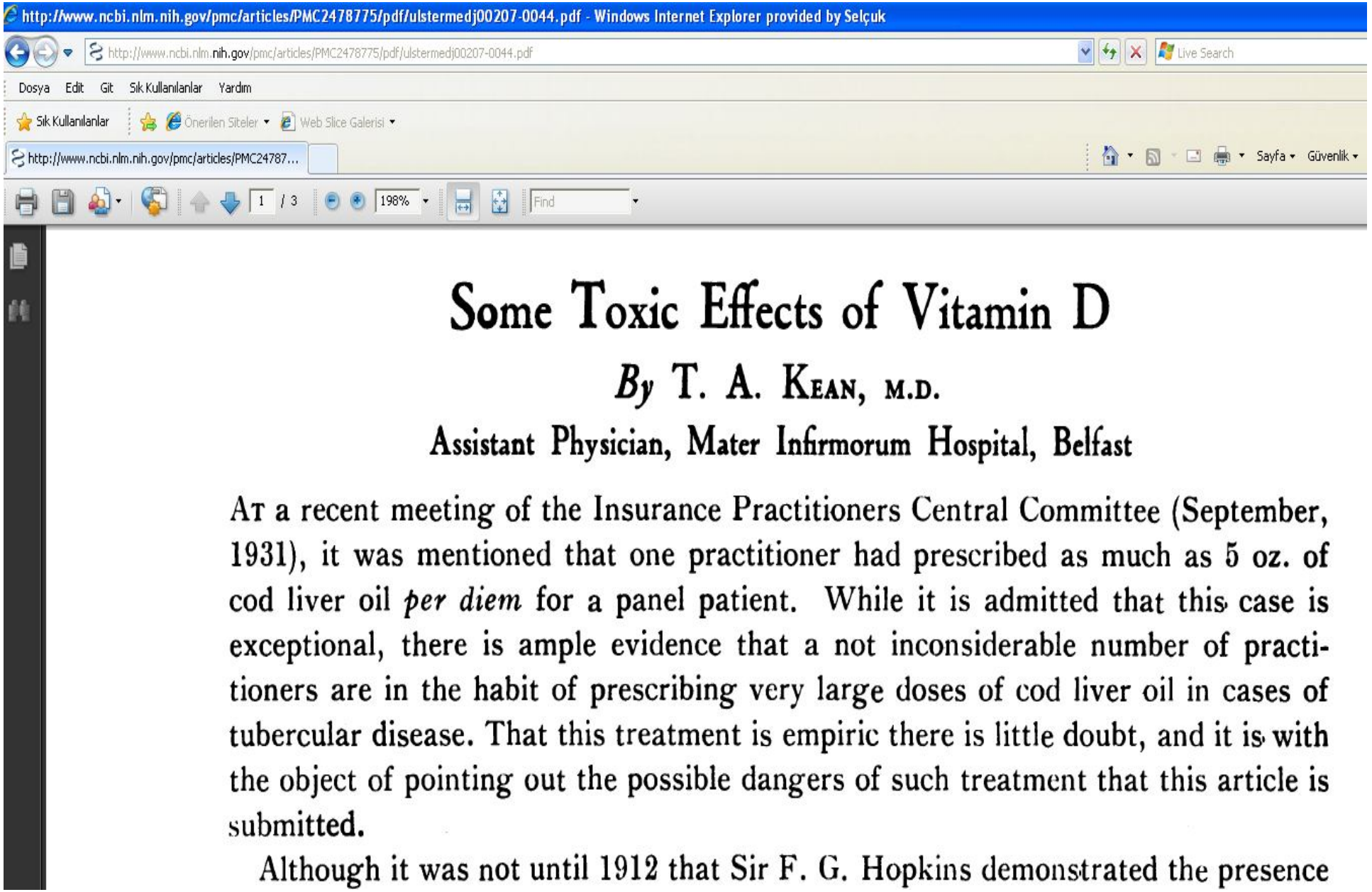
By HAROLD KING, OTTO ROSENHEIM and THOMAS ARTHUR WEBSTER.

From the National Institute for Medical Research, Hampstead, N.W. 3.

(*Received February 22nd, 1929.*)

THE stability of ergosterol when present in minute amounts in ordinary cholesterol from all animal sources (brain, gallstones, blood, skin, eggs, etc.) is surprising in view of the relatively labile character of ergosterol itself. This unsuspected contamination of "pure" cholesterol was revealed in the first instance by its antirachitic activity acquired after irradiation, and is confirmed by spectrographic analysis as well as by a specific colour reaction.

Vit D Toksik Etkileri 1932, Ulster Med J



Some Toxic Effects of Vitamin D

By T. A. KEAN, M.D.

Assistant Physician, Mater Infirmorum Hospital, Belfast

AT a recent meeting of the Insurance Practitioners Central Committee (September, 1931), it was mentioned that one practitioner had prescribed as much as 5 oz. of cod liver oil *per diem* for a panel patient. While it is admitted that this case is exceptional, there is ample evidence that a not inconsiderable number of practitioners are in the habit of prescribing very large doses of cod liver oil in cases of tubercular disease. That this treatment is empiric there is little doubt, and it is with the object of pointing out the possible dangers of such treatment that this article is submitted.

Although it was not until 1912 that Sir F. G. Hopkins demonstrated the presence

Vit D Toksisite, TA Kean, 1932, Ulster Med J

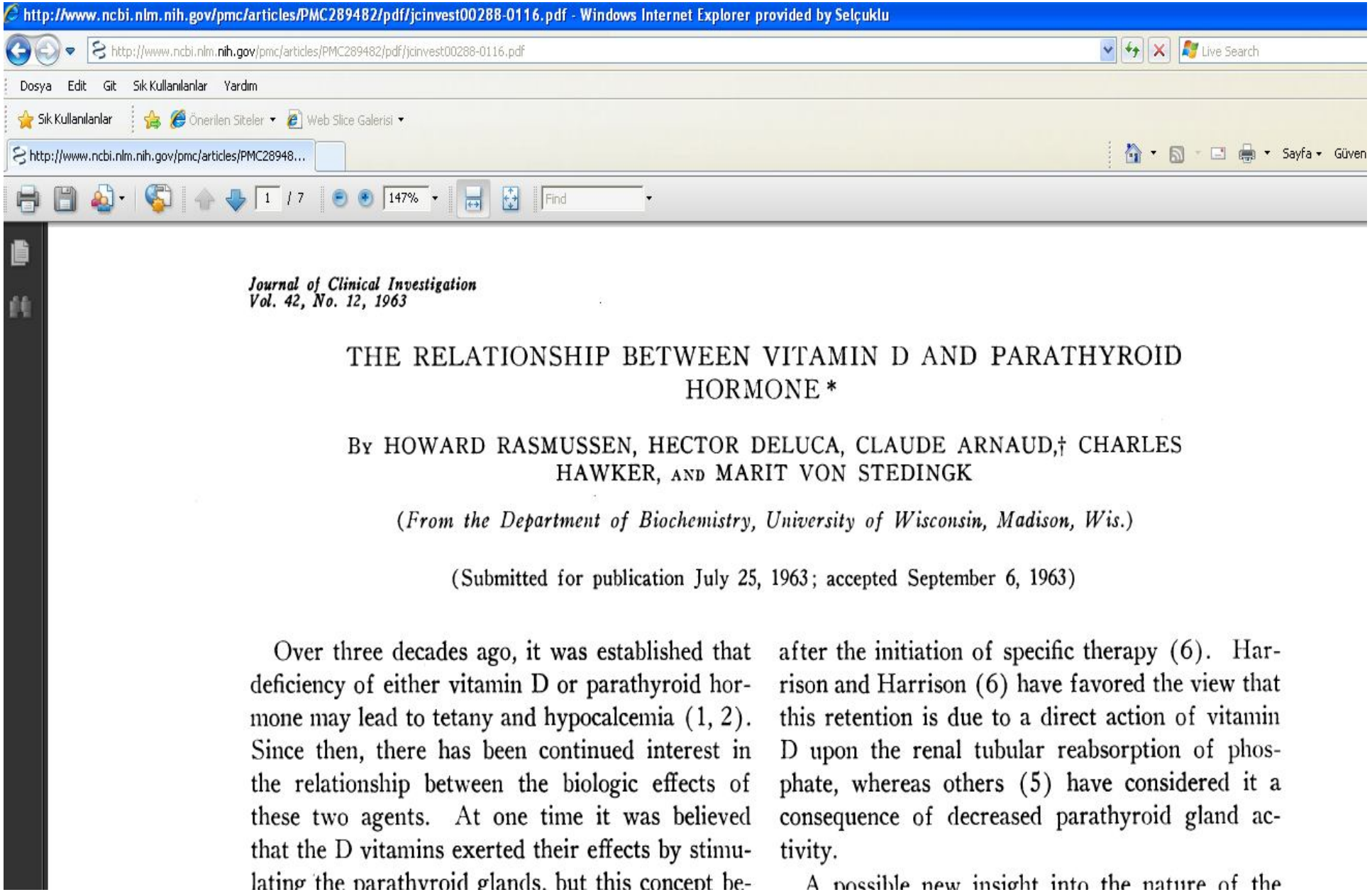
Select & Zoom

The striking evidence of the toxicity of vitamin D, however, is afforded by the experiments carried out by Robert Sœur at the Hospital for Joint Diseases, New York.

He administered, *per os*, to young guinea pigs, of medium weight, daily doses of irradiated ergosterol varying from 5,000 to 100,000 Steenbock rat-units over periods of from four to thirty-five days. (The present international standard had not then been fixed.) His general results were :—

1. A cessation of growth in all the animals.
2. A loss of weight, frequently absolute, more rarely relative (taking into account the normal increase in the control).
3. A series of morbid symptoms : diarrhœa, increase of respiratory rate, loss of vivacity, falling out of hair, and death after a time which depended on the condition of the guinea-pig and the size of the dose.
4. *The Autopsy.*—Macroscopically, little change, but treated after von Kossa's method, section of the organs revealed the presence of abnormal calcium deposits, notably in the kidney, aorta, and heart, and less marked in lungs, stomach, and intestines.
5. In five cases the guinea-pigs were killed, as their condition was precarious, and, on examination of the blood, hypercalcæmia was found in all cases (10.4 to 11.6 mg., the controls varying from 9.5 to 10.5). The normal phosphorus is about 8 mg. The animals killed during the first few days showed hyperphosphatæmia (9.5 on the fourth day); this then decreased progressively until it was only 5.5 on the thirty-fifth day.

PTH-Vit D, 1963



Journal of Clinical Investigation
Vol. 42, No. 12, 1963

THE RELATIONSHIP BETWEEN VITAMIN D AND PARATHYROID HORMONE *

By HOWARD RASMUSSEN, HECTOR DELUCA, CLAUDE ARNAUD,† CHARLES HAWKER, AND MARIT VON STEDINGK

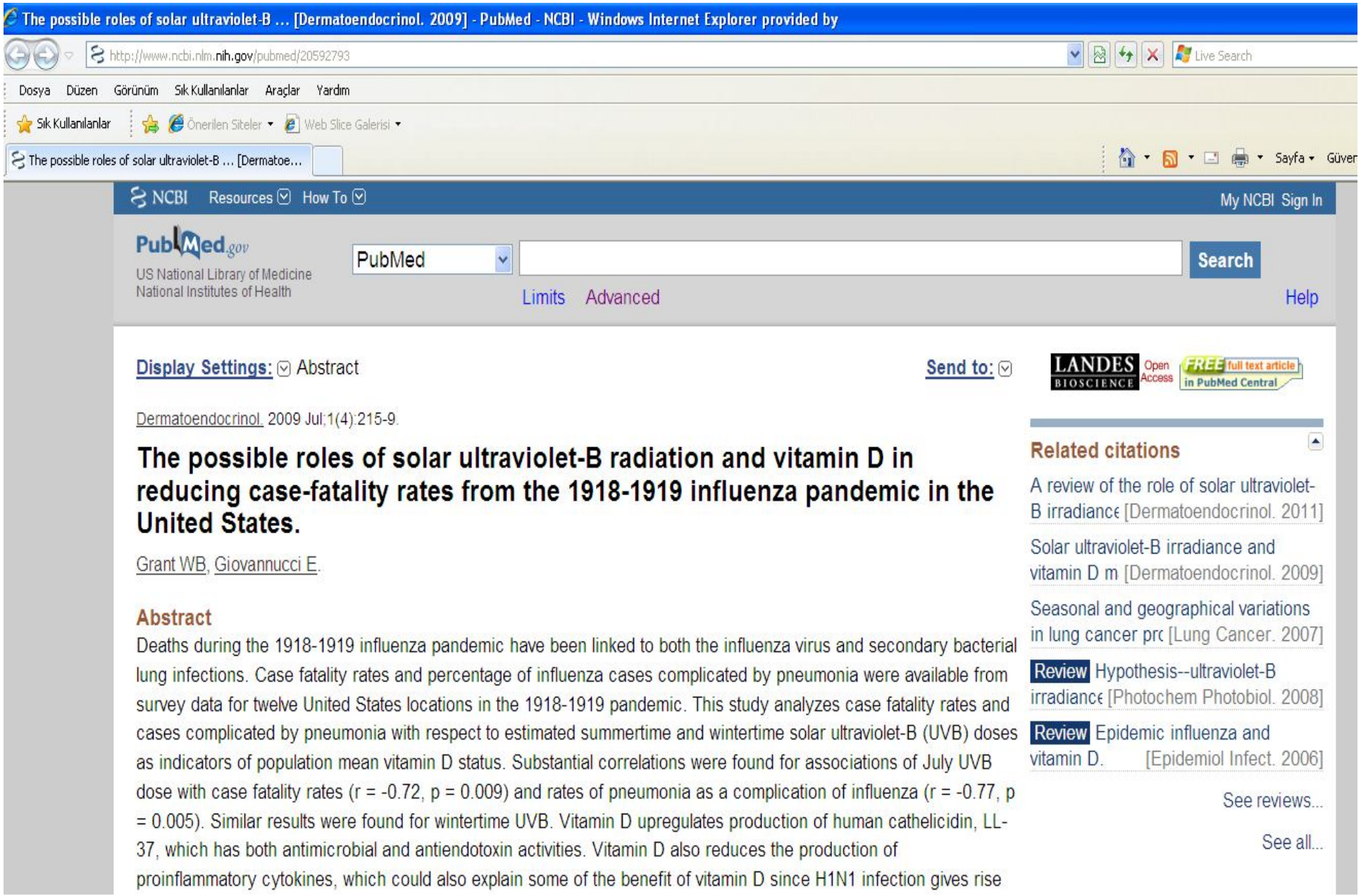
(*From the Department of Biochemistry, University of Wisconsin, Madison, Wis.*)

(Submitted for publication July 25, 1963; accepted September 6, 1963)

Over three decades ago, it was established that deficiency of either vitamin D or parathyroid hormone may lead to tetany and hypocalcemia (1, 2). Since then, there has been continued interest in the relationship between the biologic effects of these two agents. At one time it was believed that the D vitamins exerted their effects by stimulating the parathyroid glands, but this concept be-

after the initiation of specific therapy (6). Harrison and Harrison (6) have favored the view that this retention is due to a direct action of vitamin D upon the renal tubular reabsorption of phosphate, whereas others (5) have considered it a consequence of decreased parathyroid gland activity.

A possible new insight into the nature of the


The possible roles of solar ultraviolet-B ... [Dermatoendocrinol. 2009] - PubMed - NCBI - Windows Internet Explorer provided by
http://www.ncbi.nlm.nih.gov/pubmed/20592793
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Sık Kullanılanlar
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The possible roles of solar ultraviolet-B ... [Dermatoe...
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Dermatoendocrinol. 2009 Jul;1(4):215-9.
The possible roles of solar ultraviolet-B radiation and vitamin D in reducing case-fatality rates from the 1918-1919 influenza pandemic in the United States.
Grant WB, Giovannucci E.
Abstract
Deaths during the 1918-1919 influenza pandemic have been linked to both the influenza virus and secondary bacterial lung infections. Case fatality rates and percentage of influenza cases complicated by pneumonia were available from survey data for twelve United States locations in the 1918-1919 pandemic. This study analyzes case fatality rates and cases complicated by pneumonia with respect to estimated summertime and wintertime solar ultraviolet-B (UVB) doses as indicators of population mean vitamin D status. Substantial correlations were found for associations of July UVB dose with case fatality rates (r = -0.72, p = 0.009) and rates of pneumonia as a complication of influenza (r = -0.77, p = 0.005). Similar results were found for wintertime UVB. Vitamin D upregulates production of human cathelicidin, LL-37, which has both antimicrobial and antiendotoxin activities. Vitamin D also reduces the production of proinflammatory cytokines, which could also explain some of the benefit of vitamin D since H1N1 infection gives rise
Related citations
A review of the role of solar ultraviolet-B irradiance [Dermatoendocrinol. 2011]
Solar ultraviolet-B irradiance and vitamin D m [Dermatoendocrinol. 2009]
Seasonal and geographical variations in lung cancer prc [Lung Cancer. 2007]
Review Hypothesis--ultraviolet-B irradiance [Photochem Photobiol. 2008]
Review Epidemic influenza and vitamin D. [Epidemiol Infect. 2006]
See reviews...
See all...

Diyet Desteği USA

- %47 erkek, %59 bayan düzenli gıda takviyesi alıyor.
- FDA tarafından gıda takviyeleri Gıda Takviye Yönetmeliğine (FAP) düzenleniyor.
- FAP; Vitamin D eklenen gıdaları;
  - GRAS (genellikle güvenli kabul edilen) durum; mısır-buğday gevreği, süt, süt ürünleri, margarin
  - GRAS olarak kabul edilmeyen; portakal suyu
- 53 milyar $/yıl endüstri
- D Vitamini
  - 50 milyon $/yıl 2005
  - 550 milyon $/yıl 2010

Antioksidan Takviyesi

- 67 Randomize çalışma
- 232550 katılımcı,
- Antioksidan takviyesi mortalite oranını arttırıyor (RR 1.05, 95% CI 1.02 to 1.08)

- Tek tek değerlendirildiklerinde;
  - Artmış mortalite;
    - vitamin A (RR 1.16, 95% CI 1.10 to 1.24)
    - beta-carotene (RR 1.07, 95% CI 1.02 to 1.11)
    - vitamin E (RR 1.04, 95% CI 1.01 to 1.07)
  - Değişiklik yok
    - vitamin C (RR 1.06, 95% CI 0.94 to 1.20)
    - selenium (RR 0.90, 95% CI 0.80 to 1.01)

- Cochrane Database Syst Rev. 2008 Apr 16;(2):CD007176. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Bjelakovic G, Bjeark

Alfa Tokoferol-Beta Karoten

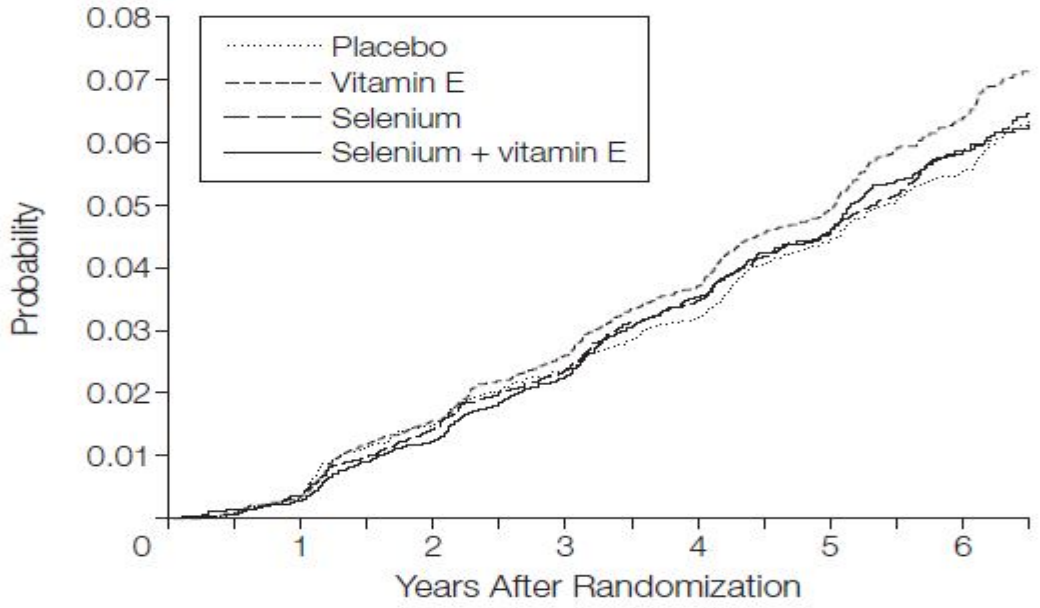
- 1996 başlangıç, 2 büyük Klinik deneme;
  - 1. Çalışma; Beta karoten supplementasyonu akciğer Ca ve kalp hastalıkları riskini arttırıyor. (Finlandiya, 29133 erkek, 50-69 yaş, 876 AC Ca, Beta-karoten alan grupta %18 yüksek oranda Ac Ca gelişme oranı, %8 artmış mortalite).
  - Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Trial (ATBC Cancer Prevention Study Group, 1994) NEW ENGLAND JOURNAL OF MEDICINE 330: 1029-1035 APR 14 1994
  - 2. çalışma; 12 yıl sonra sonuçlanıyor, plasebodan bir fark yok.

Vitamin E

- 1990'lı yılların antikanser ajanı;
  - 2008; 35000 kişiye uygulanan vit E ve selenyum supplementasyonu. 5,5 yıllık takip sonrası erken sonlandırılıyor. **The Selenium and Vitamin E Cancer Prevention Trial (SELECT)**
    - Takviye alan grup kontrol grubuna göre daha yüksek prostat kanser riskine sahip (risk oranı: 1,13, vitamin E kullanan grup)
    - *Lippman SM, et al Effect of selenium and vitamin E on risk of prostate cancer and other cancers.* ***JAMA*** *2009;301:39-51.*

SELECT Prostat Ca

Figure 2. Cumulative Incidence of Prostate Cancer Detected Each Year by Intervention Group

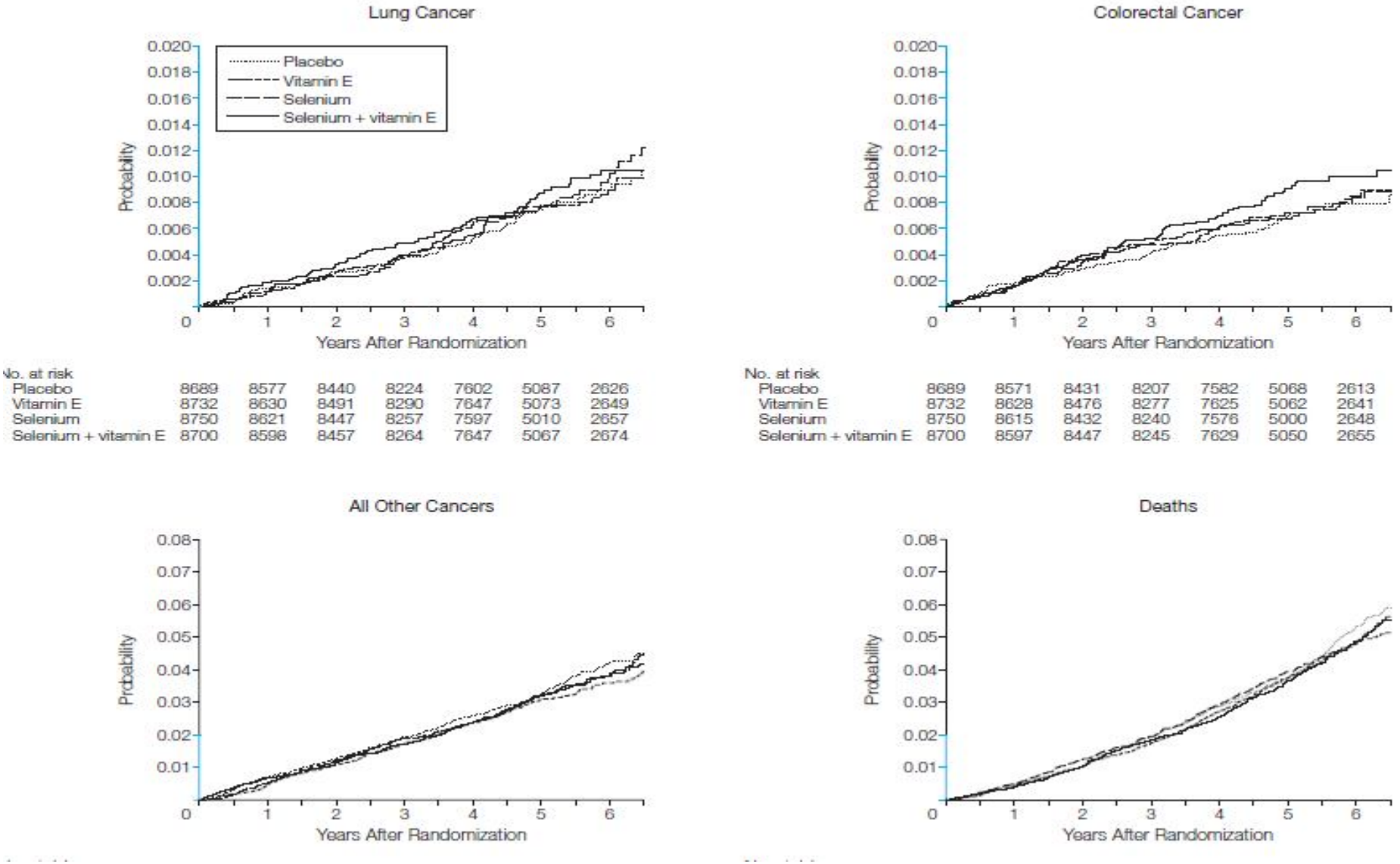


No. at risk							
Placebo	8689	8553	8328	8039	7389	4892	2516
Vitamin E	8732	8610	8373	8098	7401	4867	2537
Selenium	8750	8597	8341	8083	7393	4848	2558
Selenium + vitamin E	8700	8585	8371	8097	7428	4894	2580

Compared with placebo, there was a statistically nonsignificant increase in prostate cancer in the vitamin E group (P=.06) and not in the selenium + vitamin E group (P=.52) or the selenium group (P=.62).

SELECT

Figure 3. Cumulative Incidence of Lung Cancer, Colorectal Cancer, All Other Primary Cancers, and Deaths by Intervention Group



Folik asit

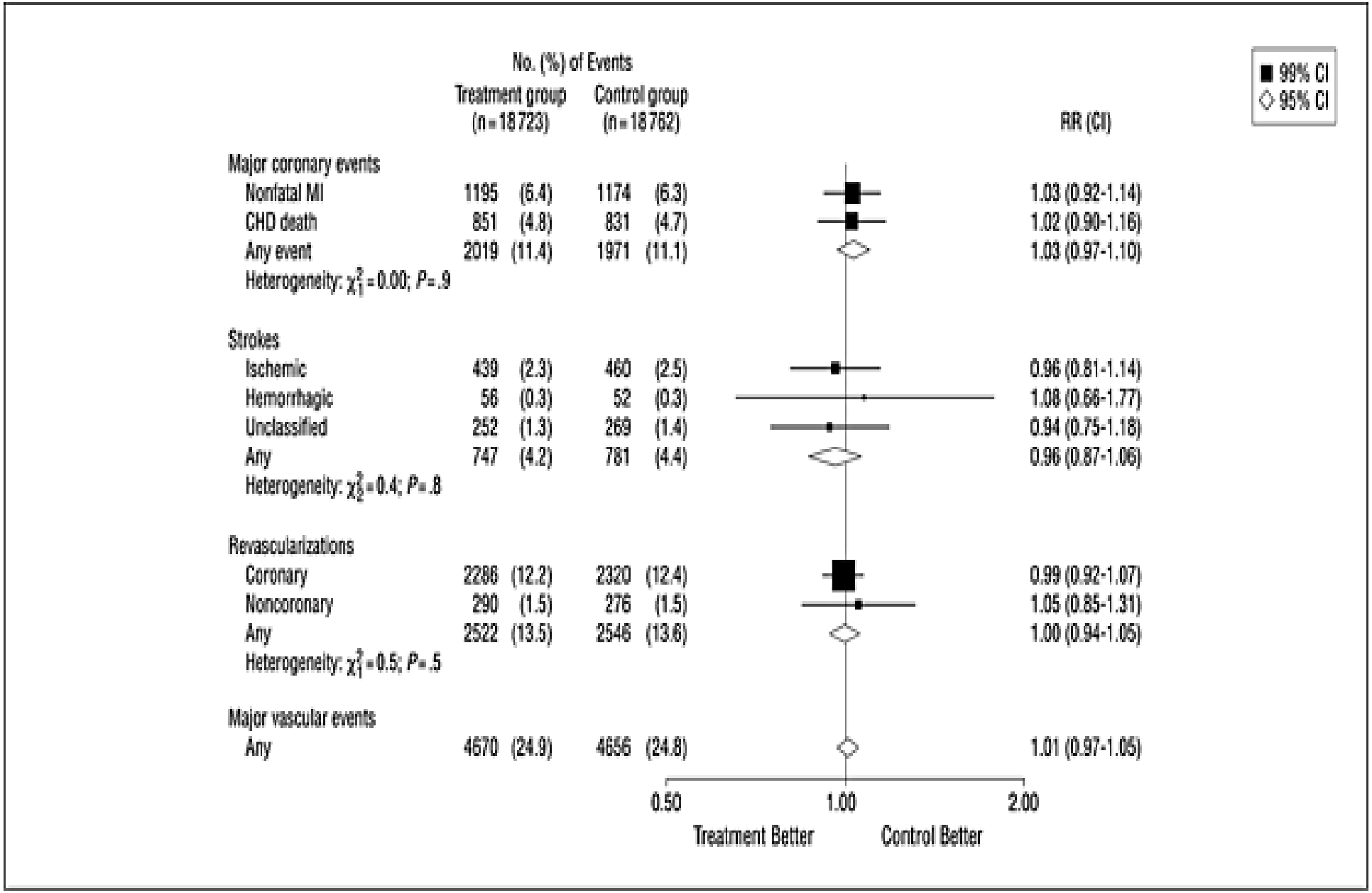
- **37485 kişi, 5 yıllık takip ve folat takviyesi**
- **Folik asit takviyesi ile ortalama 2 kat serum folat düzey artışı ve %25 Homosistein seviyesinde azalma**
- **9058 Koroner arter hastalığı, 1528 serebral vasküler hastalık, 3010 kanser, 5125 ölüm**

- **5 yıllık periyotta kardiovasküler hastalık, tüm kanser tipleri ve mortalite oranlarında hiçbir değişiklik yok.**

- *(Arch Intern Med.* 2010;170(18):1622-1631)

Effects of Lowering Homocysteine Levels With B Vitamins on Cardiovascular Disease, Cancer, and Cause-Specific Mortality Meta-analysis of 8 Randomized Trials Involving 37 485 Individuals

Robert Clarke, FRCP….. for the B-Vitamin Treatment Trialists' Collaboration (*Arch Intern Med.* 2010;170(18):1622-1631)



Vitamin C

- Vit C takviyesi, 1997-2007 arası
- 14 641 erkek doktor, 50 yaş üstü
- 1008 prostat kanser, 1943 diğer kanser.
- Vitamin C takviyesinin sağlığa herhangi bir katkısının olmadığı

- The Physician Health Study (Gaziano et al 2009 JAMA 301:52-62)

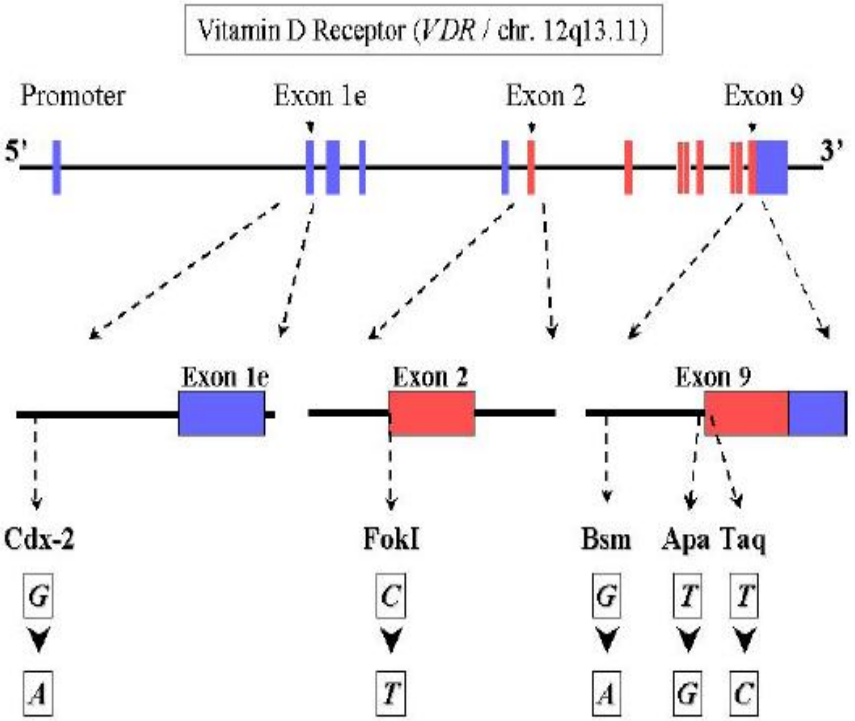
Vit D-Kanser-Gen Etkileşimi

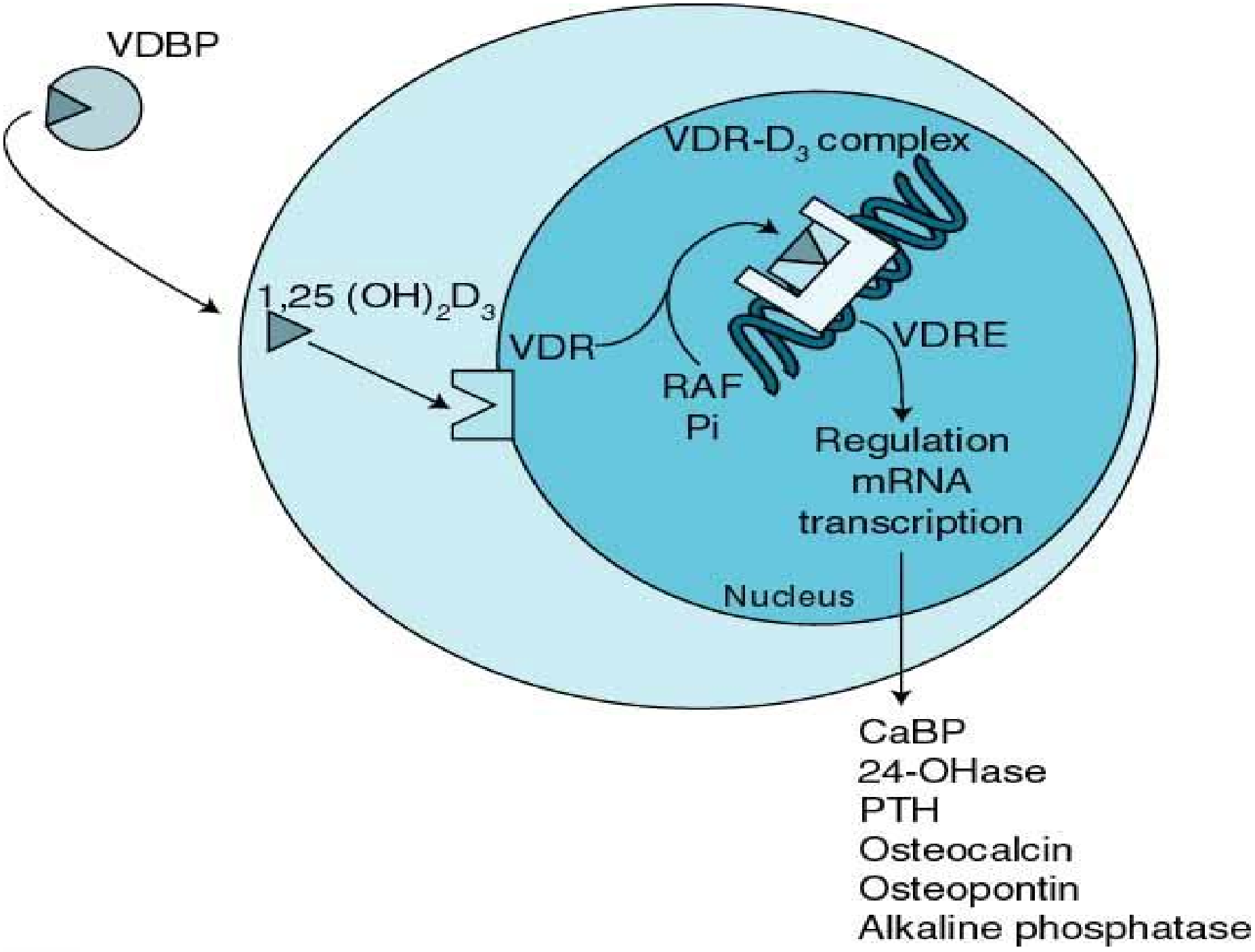
- Vitamin D ile kanser arasında ilişki;
  - 1, 25 (OH) Vit D'nin ekstrarenal üretiminin anlaşılması
  - D vitamin reseptörü (VDR) bir çok dokuda bulunması

- Vit D VDR ile bağlanması ile VDR ve retinoid X reseptör birleşir (RXR). Bu birleşme transkripsiyonel aktivite için gereklidir. Heterodimerizasyon ile Vit D-VDR-RXR nükleusda Vit D Response element (VDRE) olarak adlandırılan gen bölgesine bağlanarak gen aktivasyonunu başlatır.
- Ek yardımcı proteinler ve etkileşimler ile insan genomunun yaklaşık %3 düzenler.

VDR

- VDR 12. kromozom üzerinde bulunur ve 75 kb . 14 ekzon içerir. Exon 2-3 DNA bağlama, 7,8,9 D vitamini bağlar.
- SNP;
- • Cdx2 (1e-1739G>A)
- • FokI (exon2-Thr2Met)
- • BsmI (IVS8+284G>A)
- • ApaI (IVS8-48T>G)
- • Taq1 (exon10-Ile352Ile)




VDBP
VDR-D3 complex
1,25 (OH)2D3
VDR
RAF
Pi
VDRE
Regulation
mRNA
transcription
Nucleus
CaBP
24-OHase
PTH
Osteocalcin
Osteopontin
Alkaline phosphatase

VDR-aracılıklı veya bağımsız anti-neoplastik aktiviteler

- Vit D 2 yolla etki gösterir;
  - VDR aracılığı ile genomik transkripsiyon
  - VDR bağımsız Non-genomik etki (jejunumda hızlı Ca emilimi)

- En az 8 kanser ile ilgili sinyal yolağı Vit D tarafından etkilenir
  - Suprafizyolojik konsantrasyonlar hücre siklusunu etkiliyor (G0/G1faz)

- Moleküler mekanizma kompleks (up, down regülasyon);
  - p19, p21, p27;
  - TGFβ,
  - IGF-BP3;
  - c-myc, jun, c-fos
  - EGF receptor
- Bazı malign hücreler VDR bağımsız formda regüle edilebiliyor.

Vit D-Fox O

- FoxO (forkhead box O) proteinleri;
  - Tümör suppressor
  - Hücre proliferasyon kontrolü
  - MAPK ile inhibe ediliyor.
- 1, 25 $(OH)_2$ Vit D3 uygulaması ile VDR ile hem FoxO ailesi hemde FoxO düzenleyicisi (sirtuin1) ve protein fosfataz 1 ile bağlanarak FoxO proteinlerinin DNA bağlanmasını düzenliyor. Sirt1 ve protein fosfataz MAPK aktivitesini durduruyor.

Vit D Hücre Siklus Proteinleri

- Vit D
  - Direk regülasyon;
    - CDK1 sentezi bloke (Prostat ca cell line)
    - RBL2 ve RBBP6 (hücre siklus inhibitör protein) sentezinde artış (MCF-7, MDA-MB 231)
  - İndirek regülasyon;
    - Cyclin A, B ve F mRNA down regulation (Squamoz cancer cell line)

Vit D-IGF-1

- Vit D; IGF-1 stimüle hücrelerin proliferasyonunu IGFBP3 sentezini arttırarak inhibe ediyor (MCF-7). IGFBP3 serbest IGF1'i bağlayarak reseptörüne bağlanmasını engelliyor. IGFB3 antisense oligonükleotidler D vit aracılıklı inhibisyonu engelliyor.

Vit D TGF-β

- TGFβ
  - proliferatif-mezenkimal hücreler
  - Anti-proliferatif-epitelyal hücreler
- Vit D uygulaması
  - TGFβ2 mRNA ↑
  - TGFβ ve reseptör ↑
  - GDF-15 ve BMP ↑

Vitamin D Mortalite

- 50 çalışma, toplam; 98148 katılımcı,
- Yüksek gelir düzeyine sahip ülkeler,
- Ortalama yaş 74, %79 bayan.
- Median Vit D takviyesi 2 yıl
- Vit D3 takviyesi mortaliteyi %6 azaltıyor,
- Hiperkalsemi ve böbrek taş ihtimali artıyor.

Bjelakovic G, arkadaşları Cochrane Database Syst Rev. 2011 Jul 6;(7):CD007470. Vitamin D supplementation for prevention of mortality in adults.

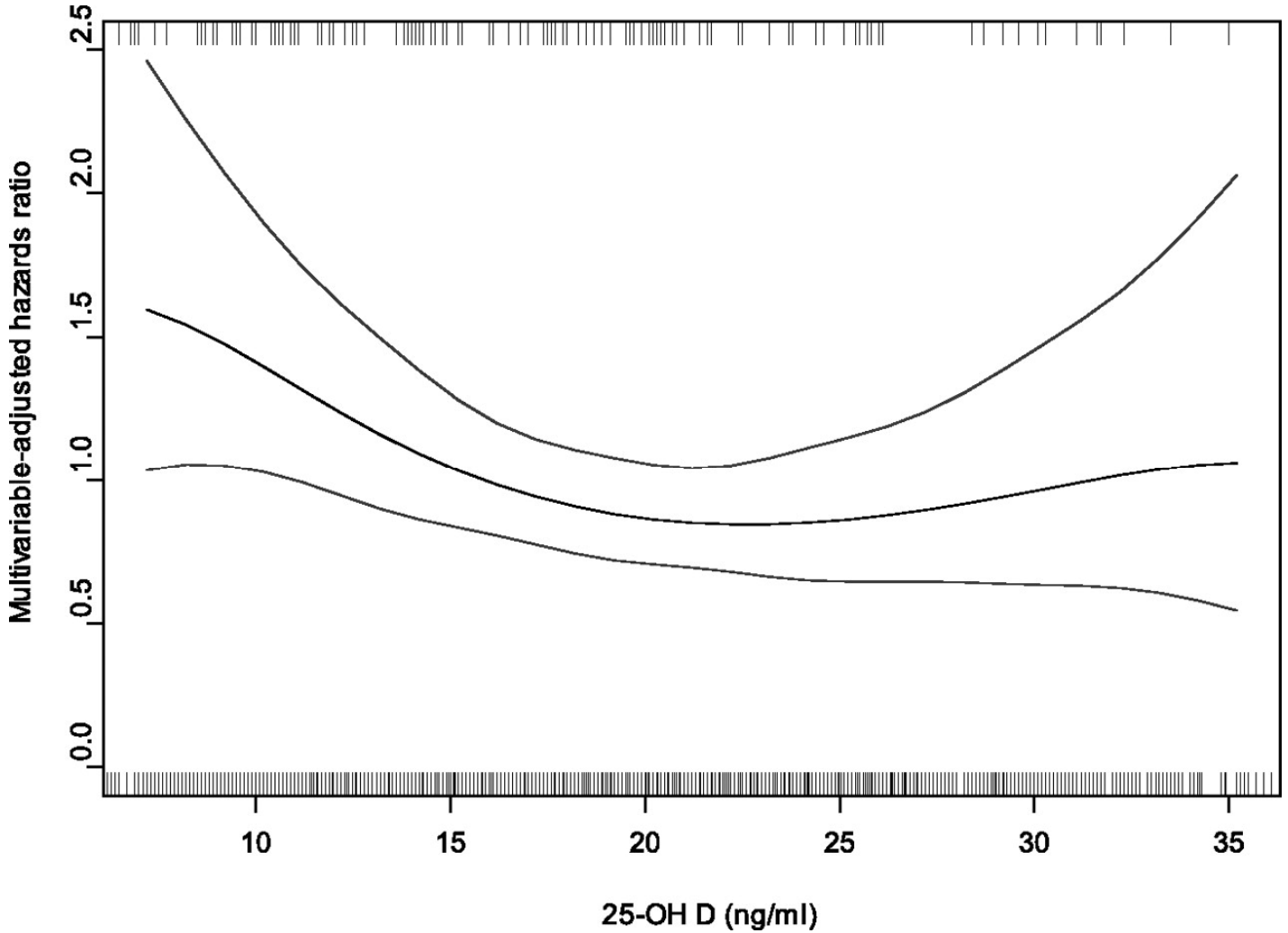
Vitamin D-Kardiovasküler Hastalıklar

- VDR ve 1α Hidroksilaz gene knockout farelerde kalp hipertrofisi, kalp yetmezliği gelişiyor.
- VDR ve 1α Hidroksilaz SNP sol ventriküler hipertrofi, kalp yetmezliği ve koroner kalsifikasyon ile ilişkili.
- Vit D uygulaması;
  - Myokardial hipertrofi geriliyor
  - MMP-9 düzeyini düşürüyor,
  - Vasküler kalsifikasyonda azalma

Vitamin D-Kardiovasküler Hastalıklar

- 1739 katılımlı Framingham Offspring Study (ort yaş 59; 55% kadın)
  - %9 Vit D eksikliği (<10 ng/ml)
  - %28 <15 ng/ml
  - 120 kişi 5 yıl boyunca koroner arter hastalığı +
  - Risk oranı <15 ng/ml->15 ng/ml için 1.62
    - <15 ng/ml +HT risk oranı 2.3
    - <15 ng/ml -HT risk oranı 1,04

Figure 2. Nonlinearity of multivariable-adjusted relation between baseline vitamin D status and incident cardiovascular events.



Wang T J et al. Circulation 2008;117:503-511

Vitamin-D Kanser

- 2008, WHO, International Agency for Research on Cancer
- VDPP (Vit D Pooling Project, 2010)
  - 10 Kohort çalışma
- Vitamin D With or Without Calcium Supplementation for Prevention of Cancer and Fractures: An Updated Meta-analysis for the U.S. Preventive Services Task Force
  Mei Chung, PhD, *Ann Intern Med.* 2011;155:827-838.
  - 19 klinik deneme ve 28 gözlemsel çalışma derlemesi.
- Instute of Medicine (IOM)i Penn State Univ

Vit D Kanser IARC

International Agency for Research on Cancer

World Health Organization

- Güneş maruziyeti ve kanser (Ekolojik ve Gözlemsel çalışmalar)
- Diyet D vitamin alımı
- Serum 25 OH D ve kanser
- Randomize klinik deneyler; Vit D, kanser ve mortalite

Güneş maruziyeti ve kanser

International Agency for Research on Cancer
World Health Organization

- Ekolojik çalışmalar;
  - Yaşanan enlem ile kanser gelişimi ve kanser mortalitesi arasında herhangi bir ilişki yok.
- Gözlemsel çalışmalar;
  - Güneş maruziyeti ile meme, prostat ve kolon arasındaki ilişki sınırlı (çalışmaların teknik eksikliği)

Diyet D Vit Alımı ve Kanser

International Agency for Research on Cancer
World Health Organization

Gıda ile vitamin D alımı ile kanser arasındaki ilişki; gıda alımındaki vit d analizlerinde ciddi hatadan dolayı güvenilir değil.

D vit içeren gıdaların fazla alınması sonucunda Kolon kanserinden korunma ile ilgili datalar sınırlı.

Prostat kanseri ve meme kanseri ile ilgili sonuçlar negatif.

Serum 25 OH D ve kanser

International Agency for Research on Cancer
World Health Organization

- Kolon kanserinde anlamlı koruyuculuk;
  - plazma 25(OH)D konsantrasyonunda 1-ng/mL artış RR : 0.984, (95% CI: 0.976, 0.991)*.
- Meme kanseri istatistiksel fark yok;
  - relative risk 0.994, 95% CI: 0.964-1.024).
- Prostat Kanseri fark yok.

Randomize klinik deneyler; Vit D, kanser ve mortalite

International Agency for Research on Cancer

World Health Organization

- 3 çift-kör, plasebo kontrollü çalışma; 10 - 21µg günlük D vitamin takviyesinin kanser insidansında herhangi bir etkisi yok.
- 18 RCT 12 -15 µg D vit takviyesi mortalite oranını azaltıyor.
- 2 RCT; Vitamin D kanser insidansından daha çok kanser mortalitesi üzerine etkisi var.

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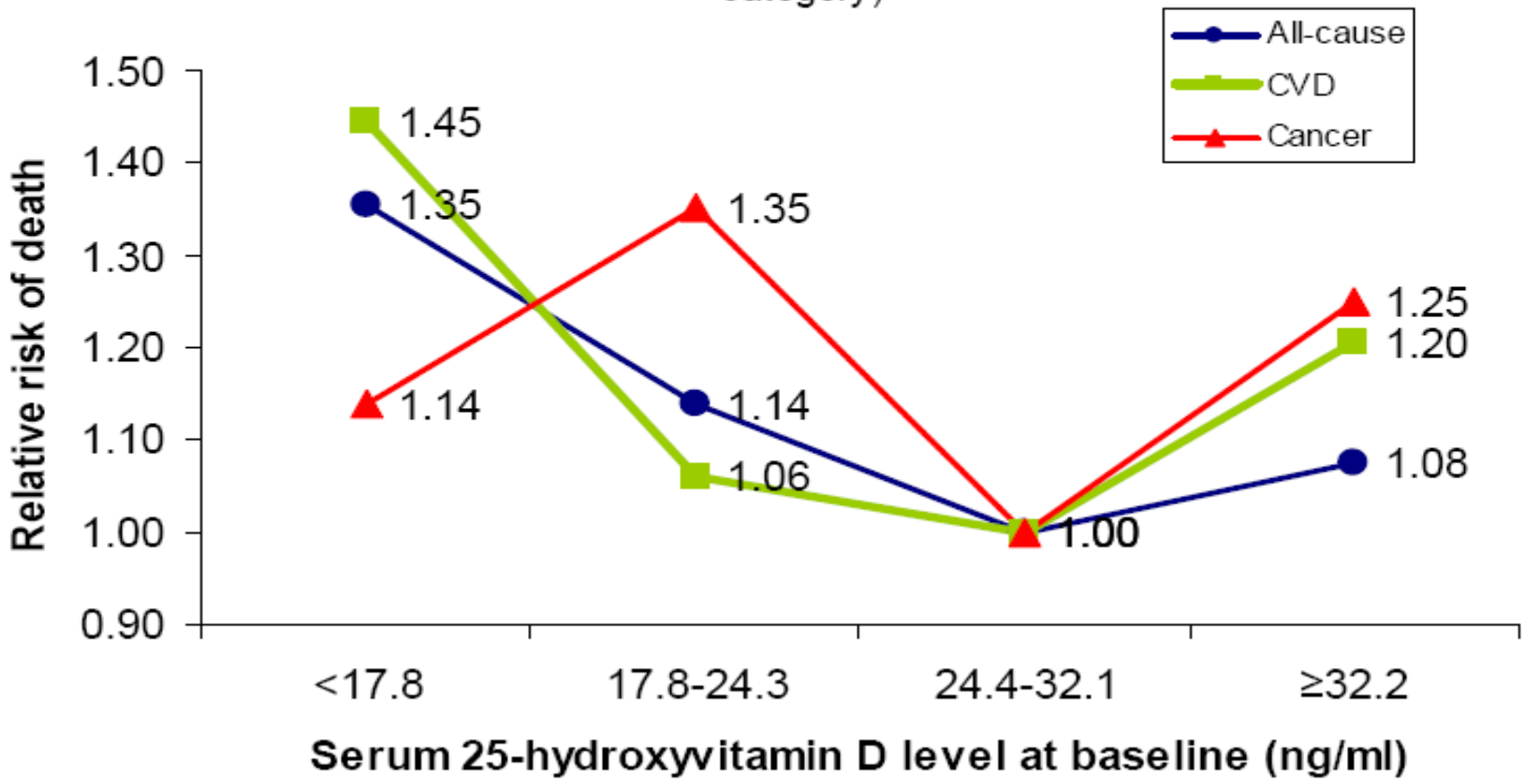
Figure 12.2 - Relative risk of dying from all-cause, cardiovascular disease (CVD) or cancer in the NHANES III study according to serum 25-hydroxyvitamin D level at baseline (24.4 to 32.1 ng/ml is the reference category)



Instute of Medicine (IOM), Penn State Un

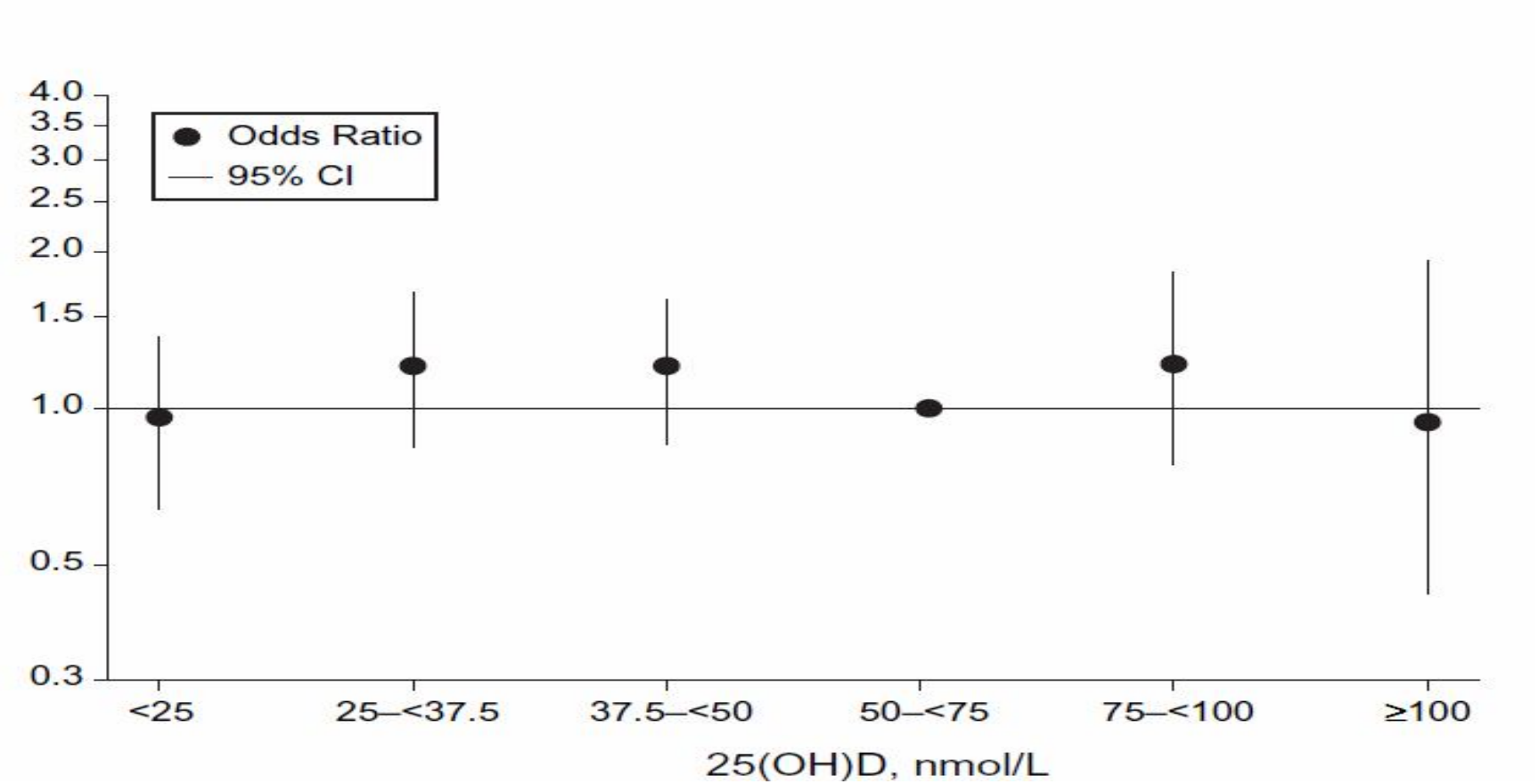
- Yaklaşık 1000 adet rapor incelenmesi sonucu;
  - Kemik sağlığı konusunda Vit D etkisi gerçek; raşitizm, osteomalazi ve osteoporoz konusunda etkili.
  - Kemik dışı faydaları sonuçsuz.

(J Clin Endocrinol Metab. 2011 January; 96(1): 53–58.)

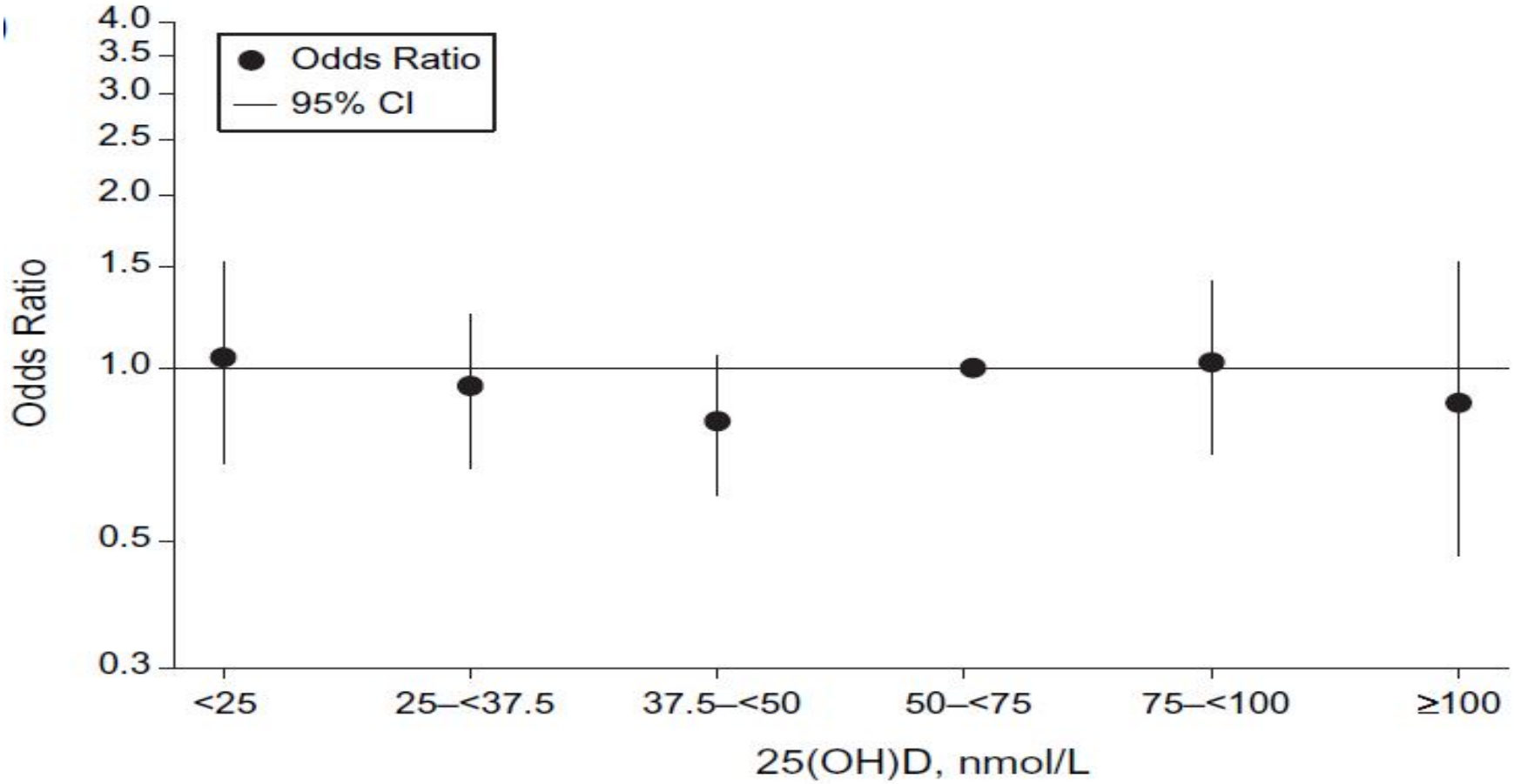
Vit D - Nadir Kanserler

- VDPP (Vit D Pooling Project) Konsorsiyum, 10 Cohort çalışmayı inceledikten sonra;
  - Yüksek Vit D dozlarının nadir kanserlerden koruma üzerine herhangi bir etkinliği olmadığı,
  - Düşük dozların herhangi bir koruyuculuğu olmadığı,
  - >100 ng/ml üzerindeki Vit D dozunun pankreas kanser için OR 2.12 (95% CI 1.23-3.64).

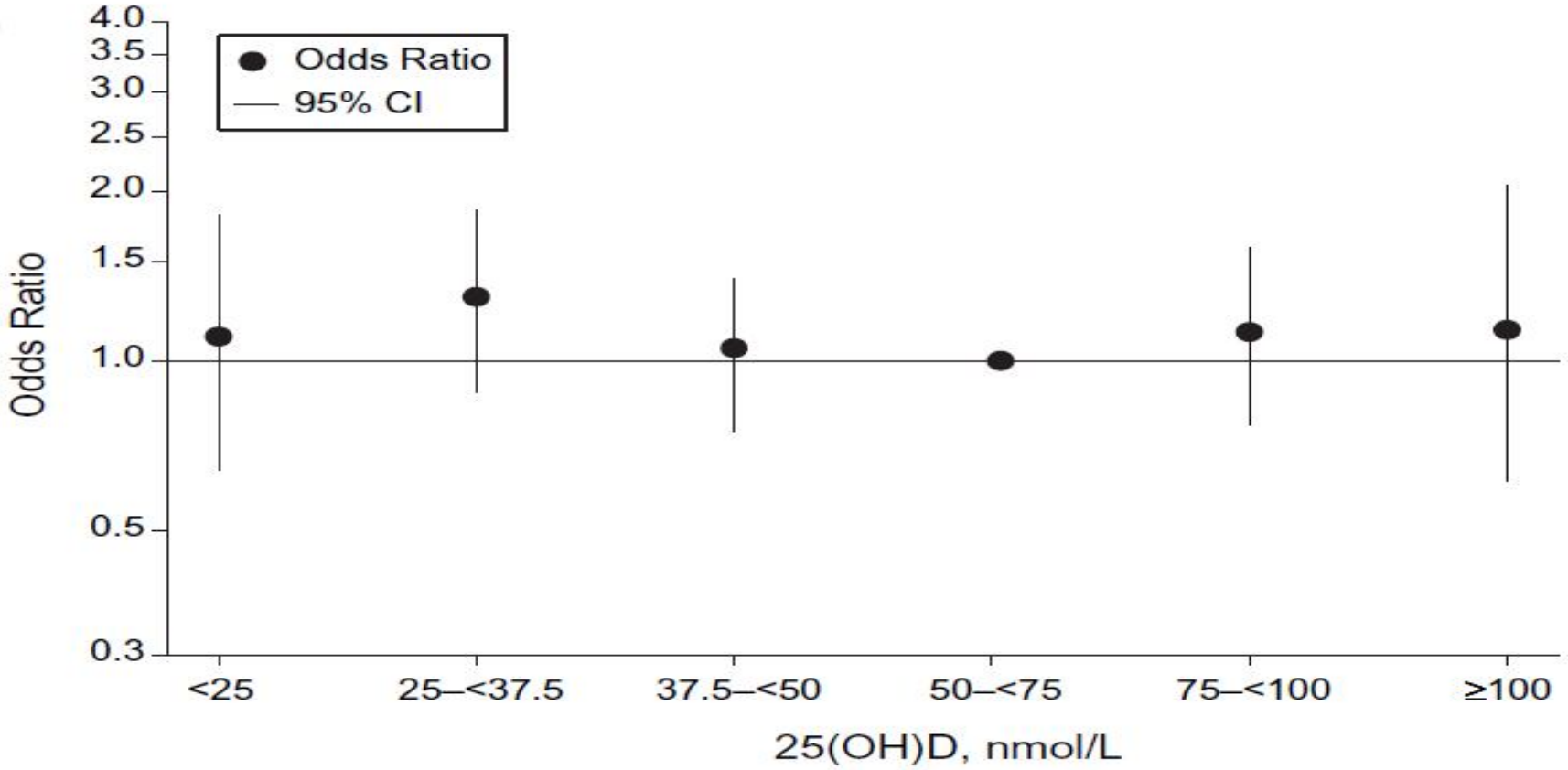
Vit D Renal Kanser



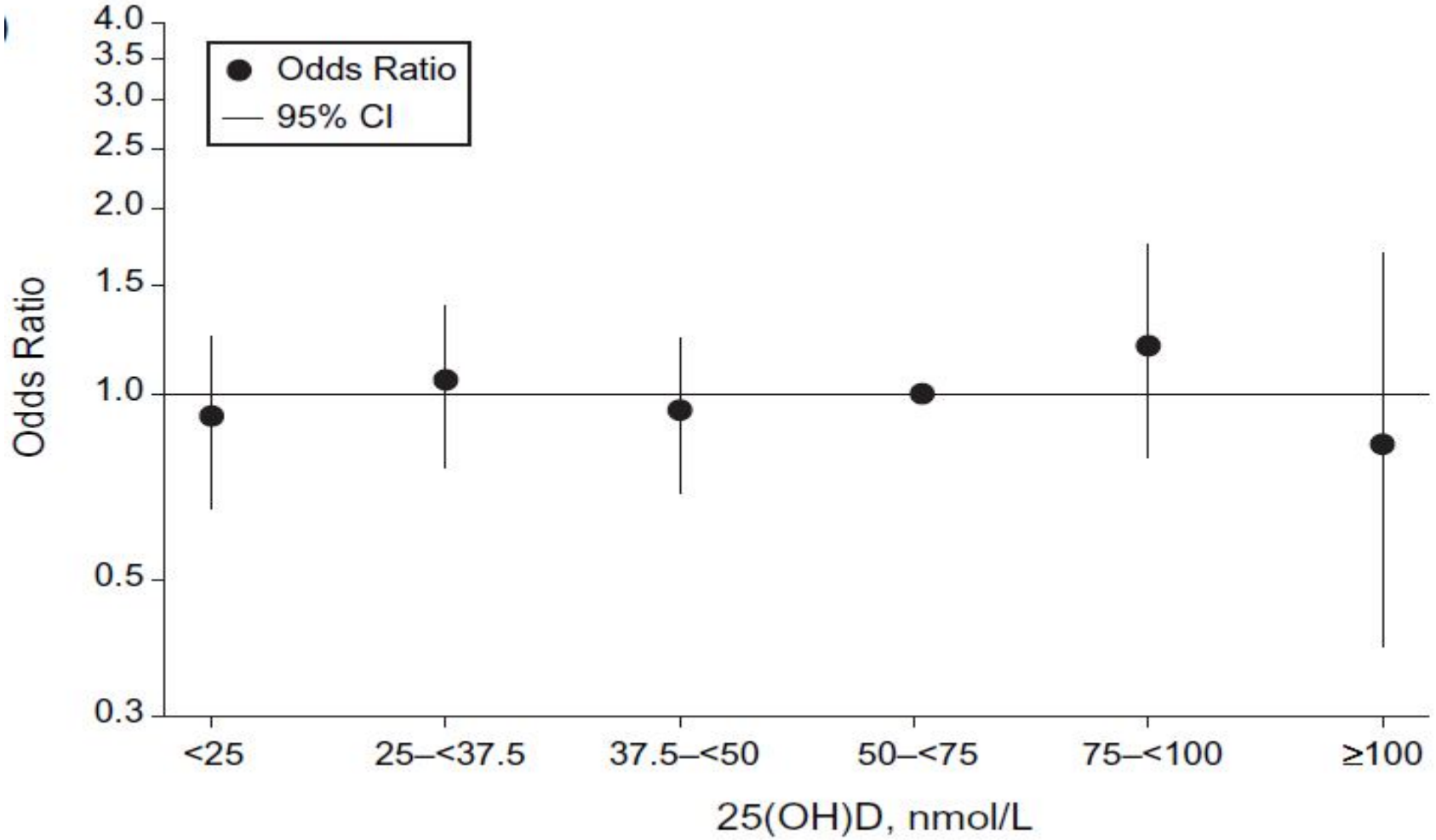
Endometrial Kanser



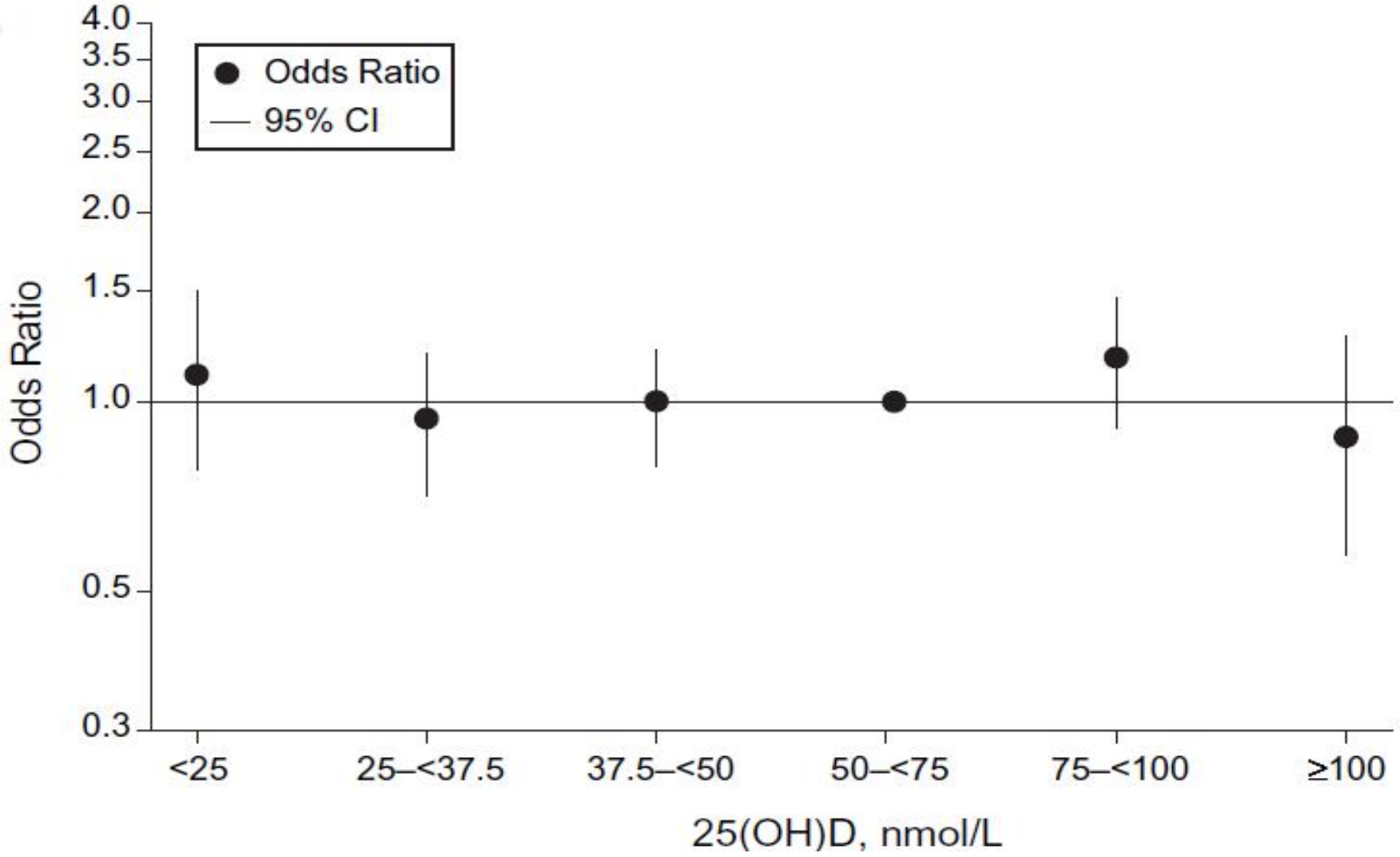
Over Kanseri



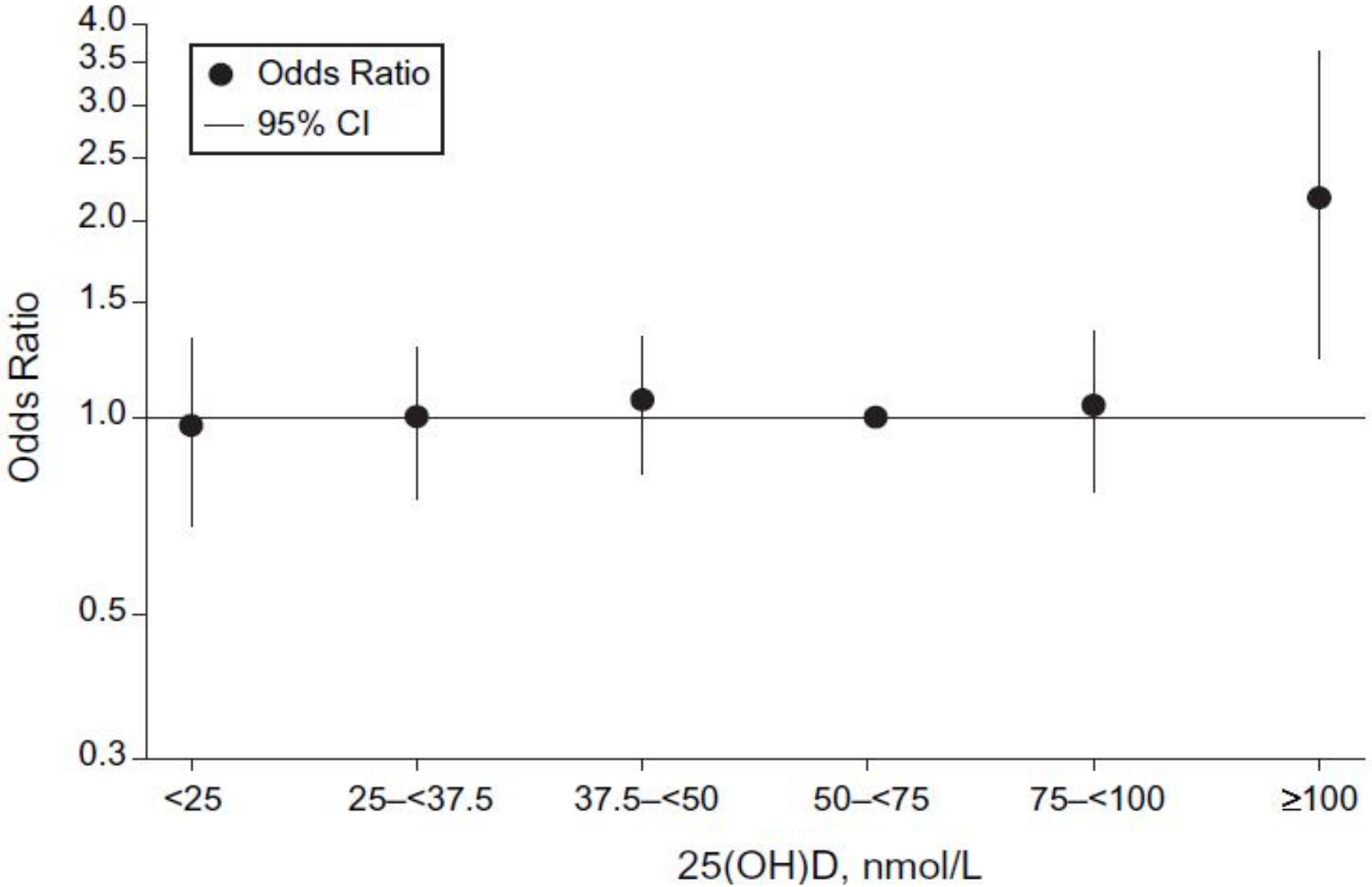
Mide-Ösefagus Kanserleri



Non-Hodgkin Lenfoma



Pankreas Kanseri



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KQs and Comparisons of Interest	Outcomes	Studies (Total Sample Size)	Methodologic Quality	Follow-up Duration	Main Findings	Supplement or Appendix Figure Providing Details
KQ 1: What are the effects of vitamin D with or without calcium supplements on the clinical outcomes of cancer and fractures in RCTs? (overarching question)						
Vitamin D supplementation vs. placebo*	Total cancer	2 RCTs (n = 3577)	2 fair	4–5 y	1 RCT in elderly men and women, aged ≥71 y (n = 2686) Incidence: HR, 1.09 (95% CI, 0.86–1.36) Mortality: HR, 0.86 (CI, 0.61–1.20) 1 RCT in postmenopausal women, aged >55 y (n = 891)† Incidence: RR, 0.76 (CI, 0.86–1.55) Mortality: RR, 0.55 (CI, 0.24–1.28)	Supplement 1
	Colorectal cancer	1 RCT (n = 2686)	1 fair	5 y	Incidence: HR, 1.02 (CI, 0.60–1.74) Mortality: HR, 0.62 (CI, 0.24–1.60)	Supplement 1
	Breast cancer	1 RCT (n = 2686)	1 fair	5 y	Incidence: HR, 0.99 (CI, 0.25–4.0) Mortality: NR	Supplement 1
Combined vitamin D and calcium supplementation vs. placebo	Total cancer	2 RCTs (n = 37 016)	1 good 1 fair	4–7 y	1 RCT in postmenopausal women, aged >55 y (n = 734)† Incidence: RR, 0.40 (CI, 0.20–0.82)‡ Mortality: RR, 0.23 (CI, 0.09–0.60)‡ 1 RCT in postmenopausal women (n = 36 282) Incidence: HR, 0.98 (CI, 0.91–1.05) Mortality: HR, 0.89 (CI, 0.77–1.03)	Supplement 1
	Colorectal cancer	1 RCT (n = 36 282)	1 good	7 y	Incidence: HR, 1.08 (CI, 0.86–1.34) Mortality: HR, 0.82 (CI, 0.52–1.29)	Supplement 1
	Breast cancer	1 RCT (n = 36 282)	1 good	7 y	Incidence: HR, 0.96 (CI, 0.86–1.07) Mortality: HR, 0.99 (CI, 0.55–1.76)	Supplement 1

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KQ 2: What are the associations between vitamin D status and the clinical outcomes of cancer and fractures in observational studies?

Dose–response relationship between 25-(OH)D concentration at baseline and risk for cancer	Total cancer	3 prospective cohort studies (n = 19 503)	1 good 2 fair	Mean, 7–14 y	Higher 25-(OH)D concentrations were associated with increased risk for total cancer mortality in men, but the ranges of 25-(OH)D concentrations varied across studies One study found that baseline blood 25-(OH)D concentration was not associated with risk for total cancer mortality in adult women (n = 8914)	Supplement 3; Supplement 4
	Colorectal cancer	9 nested case–control studies (3136 cases)	8 fair 1 poor	NA	Linear dose–response meta-analysis of 9 studies Pooled adjusted OR, 0.94 (CI, 0.91–0.97)‡ per 10-nmol/L increase in 25-(OH)D concentration	Supplement 3
	Prostate cancer	11 nested case–control studies (4005 cases)	4 fair 7 poor	NA	Linear dose–response meta-analysis of 8 studies Pooled adjusted OR, 1.01 (CI, 0.99–1.04) per 10-nmol/L increase in 25-(OH)D concentration	Supplement 3
	Breast cancer	5 nested case–control studies (3128 cases)	3 fair 2 poor	NA	Linear dose–response meta-analysis of 4 studies Pooled adjusted OR, 0.99 (CI, 0.97–1.01) per 10-nmol/L increase in 25-(OH)D concentration	Supplement 3

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KQ 3: What are the effects of vitamin D with or without calcium supplements on the net changes in vitamin D status in RCTs?

Dose of vitamin D supplement	Net changes in blood 25-(OH)D concentration	26 RCTs included in our 2009 evidence report (5)	Clear relationship between increasing dose of vitamin D_3 and increasing net change in blood 25-(OH)D concentration	Appendix Figure 7

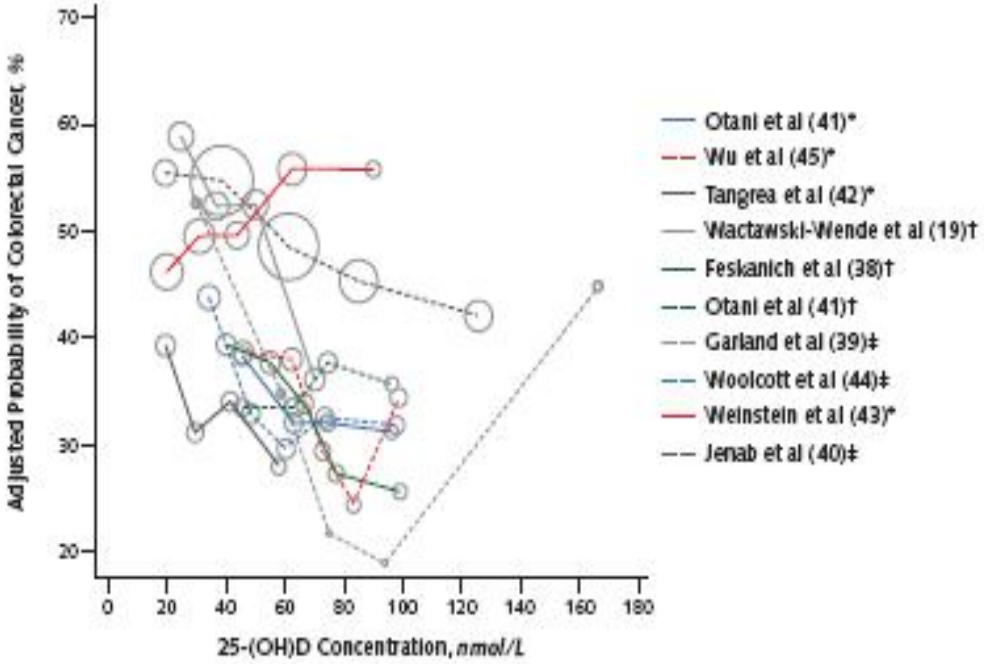
KQ 4: What are the adverse outcomes associated with vitamin D and calcium supplements in RCTs?

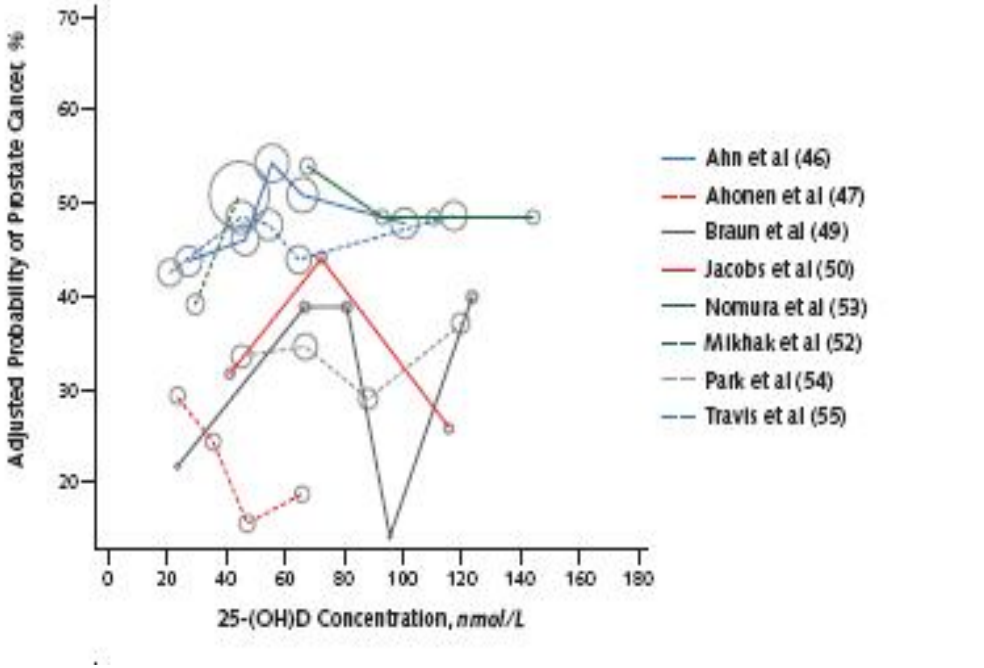
Vitamin D with or without calcium supplementation vs. placebo	Adverse events	All 63 RCTs included in our 2009 evidence report (5) and 19 RCTs included in the focused update	The majority of RCTs did not provide information on adverse events and were not adequately powered to detect adverse events. 1 RCT in postmenopausal women (n = 36 282) Renal stones: HR, 1.17 (CI, 1.02–1.34) Urinary tract stones: HR, 1.17 (CI, 1.02–1.34)	

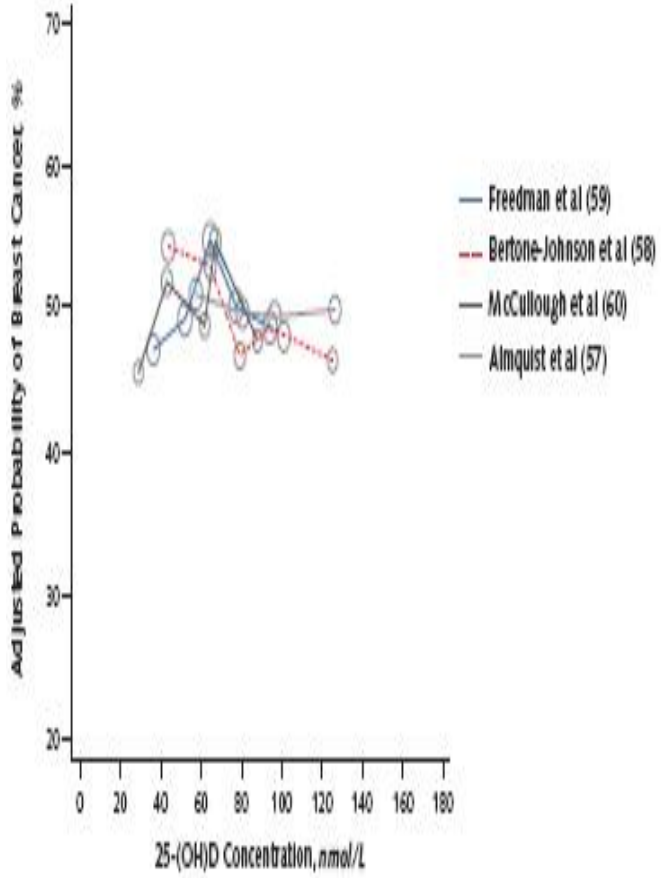
Pre-Diyagnostik D Vit Düzeyleri

Table 2. Results of Linear Mixed-Effects Meta-Regression to Examine the Dose–Response Relationships Between Each 10-nmol/L Increase in Prediagnosis Blood 25-Hydroxyvitamin D Concentration and the Risks for Colorectal, Prostate, and Breast Cancer in Nested Case–Control Studies

Outcome	Studies (References)	Methodologic Quality	Case-Patients and Controls, *n**	Pooled Adjusted OR (95% CI)†	*P* Value
Colorectal cancer	9 nested case–control studies (19, 38–45)	8 fair, 1 poor	1127 case-patients 1122 controls	0.94 (0.91–0.97)	<0.001
Prostate cancer	8 nested case–control studies (46, 47, 49, 50, 52–55)	4 fair, 4 poor	2399 case-patients 3210 controls	1.01 (0.99–1.04)	0.35
Female breast cancer	4 nested case–control studies (57–60)	3 fair, 1 poor	2363 case-patients 2363 controls	0.99 (0.97–1.01)	0.42


Adjusted Probability of Colorectal Cancer, %
70
60
50
40
30
20
0
20
40
60
80
100
120
140
160
180
25-(OH)D Concentration, nmol/L
Otani et al (41)*
Wu et al (45)*
Tangrea et al (42)*
Wactawski-Wende et al (19)†
Feskanich et al (38)†
Otani et al (41)†
Garland et al (39)‡
Woolcott et al (44)‡
Weinstein et al (43)*
Jenab et al (40)‡


Adjusted Probability of Prostate Cancer, %
70
60
50
40
30
20
0
20
40
60
80
100
120
140
160
180
25-(OH)D Concentration, nmol/L
Ahn et al (46)
Ahonen et al (47)
Braun et al (49)
Jacobs et al (50)
Nomura et al (53)
Mikhak et al (52)
Park et al (54)
Travis et al (55)


Adjusted Probability of Breast Cancer, %
70
60
50
40
30
20
0
20
40
60
80
100
120
140
160
180
25-(OH)D Concentration, nmol/L
Freedman et al (59)
Bertone-Johnson et al (58)
McCullough et al (60)
Almquist et al (57)

- Literatürler; serum 25 OHD düzeylerinin
  - 16 ng/ml (40 nmol/l) popülasyonun yarısını kapsamakta.
  - 20 ng/ml (50 nmol/l) düzeyindeki 25 OHD'nin ise popülasyonun %97.5'unu kapsamakta.
  - 50 ng/ml (125 nmol/l) üzeri Vit D düzeylerinin potansiyel yan etkiler açısından dikkatli olunması gerekli.
  - Literatürdeki en yüksek doz vit D uygulanan klinik denemede, yaşlı kadınlarda yüksek doz uygulanmasının kemiklerde kırık riskini arttırdığı rapor edilmiştir (500 000 IU tek doz uygulaması, ortalama 1370 IU/gün).

- Kanada ve USA ulusal hükümet anketleri;
  - Normal beslenme düzenleri ile yeterince Ca ve Vit D alındığı,
  - 9-18 yaş grubu daha fazla kalsiyum ihtiyacı olduğu
  - Postmenapozal kadınlarda gıda ile ~400 IU/gün D vit alınımının 20 ng/ml kan düzeyi oluşturduğu.

    ***Gıda takviye endüstrisi 600 IU/gün kullanılmasını öneriyorlar.
  - Zayıf beslenen, daha kuzey enlemlerde yaşayan, ve zencilerde 16 ng/ml (40 nmol/liter), altındaki düzeye sahip olanlar risk altında gruplar olarak değerlendirilmektedir.

- Vit D ile ilgili gözlemsel çalışmalarda vit d ile klinik sonuçlar kafa karıştırıcı ve nedeni kanıtlanamayacak formda.
- Doğru kalibrasyon araçları, gelişen metodoloji ile Vit D analizlerindeki doğruluk ve kesinlik üzerine olan endişeler gittikçe azalmaktadır.
- Vitamin D takviyesinin yarar ve zararları doğru Vitamin D düzeyini değerlendirmekteki güçlük nedeni ile zor.
  - Kullanılan yöntemler gıda takviyesi ile alınan vit D'yi endojen Vit D ile ayıramamakta.
  - Hem D vit katkılı hemde katkısız besin veritabanlarında D vit düzey belirsizlikleri ile olan kısıtlamalar.
  - Tüm D vitamin alım yolları ile alım sonucu "güvenilir seviye" aşılabilir.

- Kanser gelişiminin önlenmesi yüksek doz vitamin takviye önerilmesi ile gerçekleştirilebilecek kadar basit bir olay değil.
- Dış ortamda daha çok yürüyen, koşan, sportif aktivite yapan daha fazla güneşe maruz kalıp daha yüksek 25OHD düzeyine sahip olur.
  - Daha sağlıklı olmak için;
    - Yüksek Vit D düzeyi?
    - Yüksek fiziksel aktivite?


Teşekkürler...