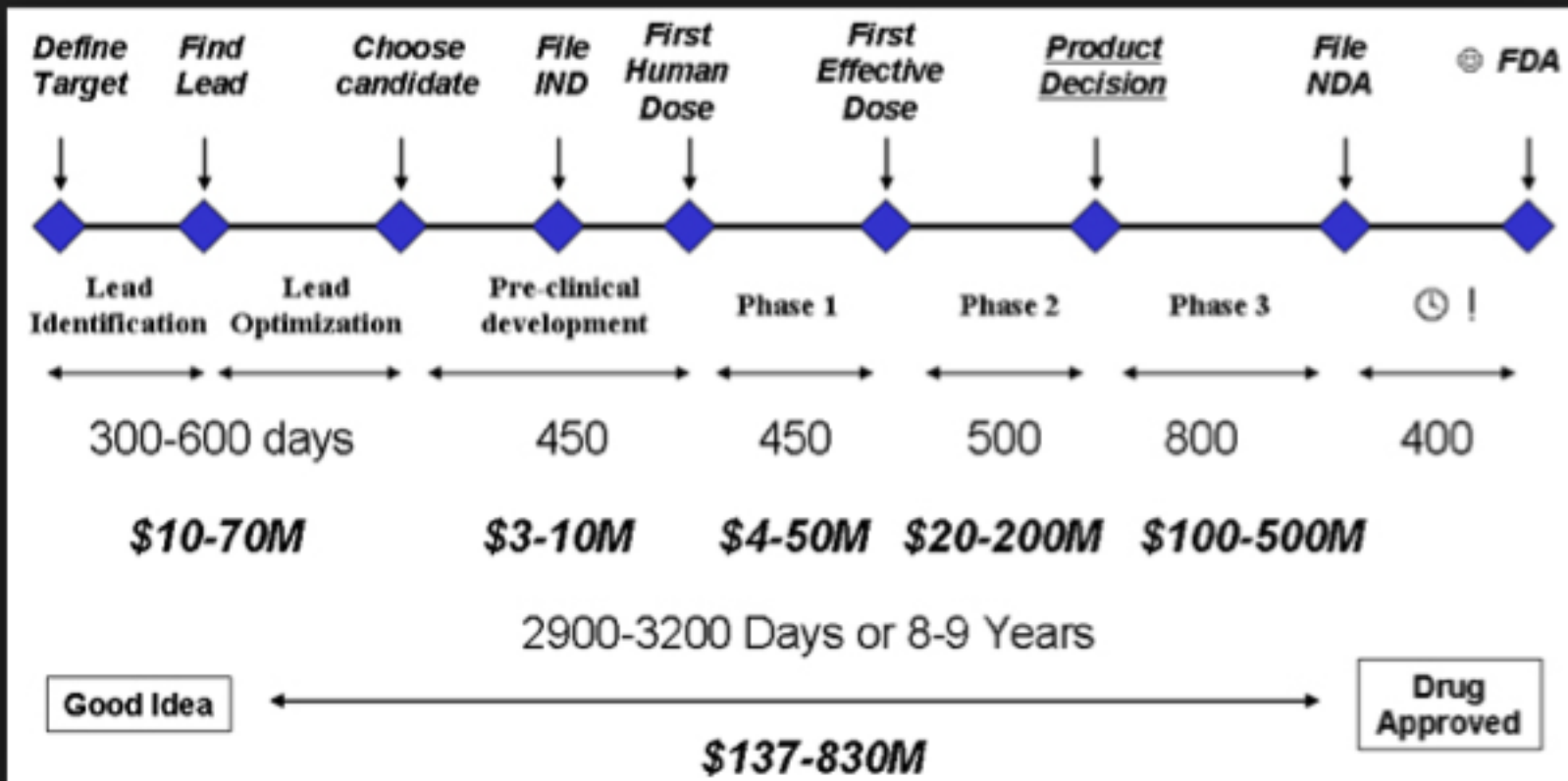
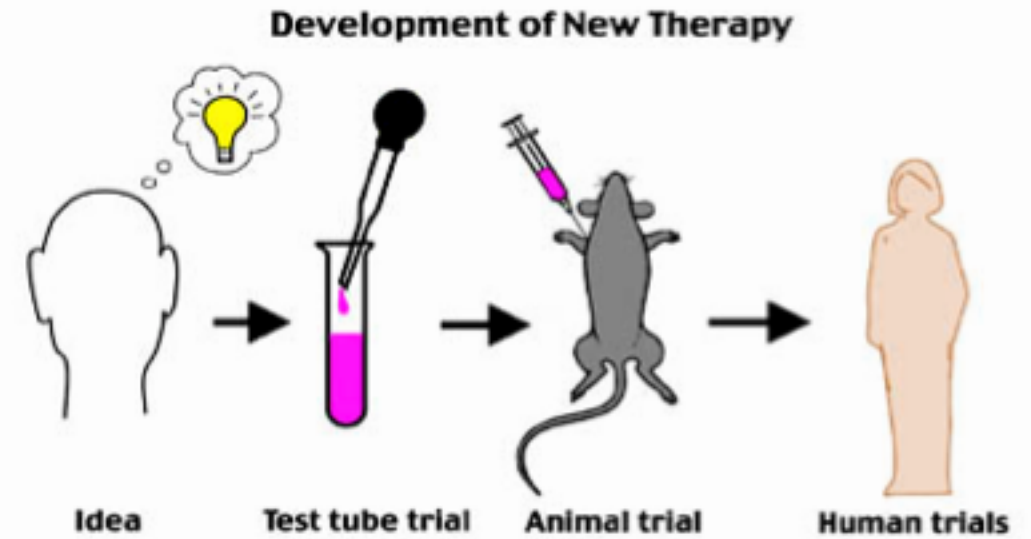


# Clinical trials, Bias/Placebo effect

## Cancer Updates



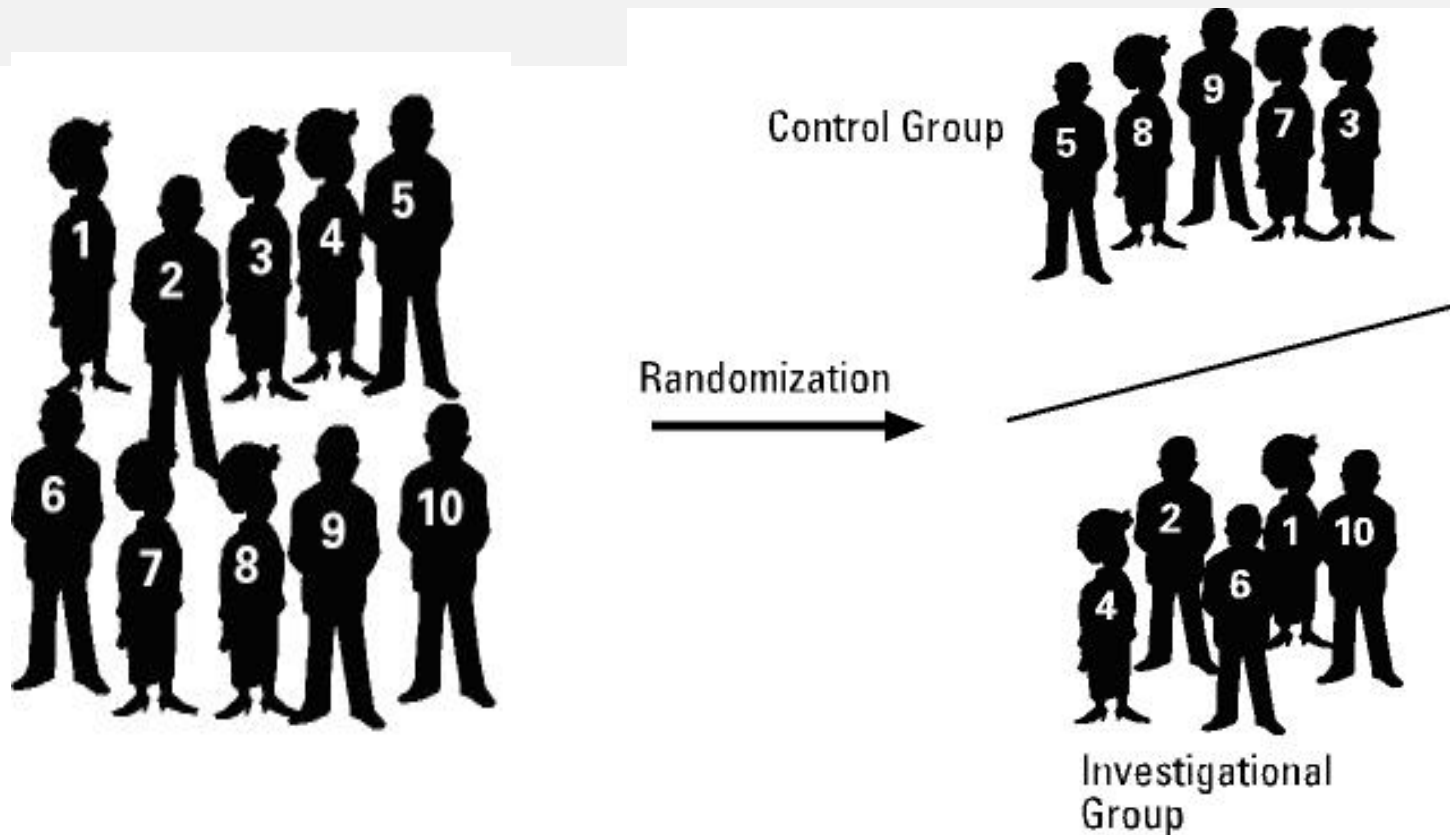
# Types of Cancer Clinical Trials

- ☐ **Treatment trials**
- ☐ **Prevention trials**
- ☐ **Early-detection trials/screening trials**
- ☐ **Diagnostic trials**
- ☐ **Quality-of-life studies/supportive care studies**



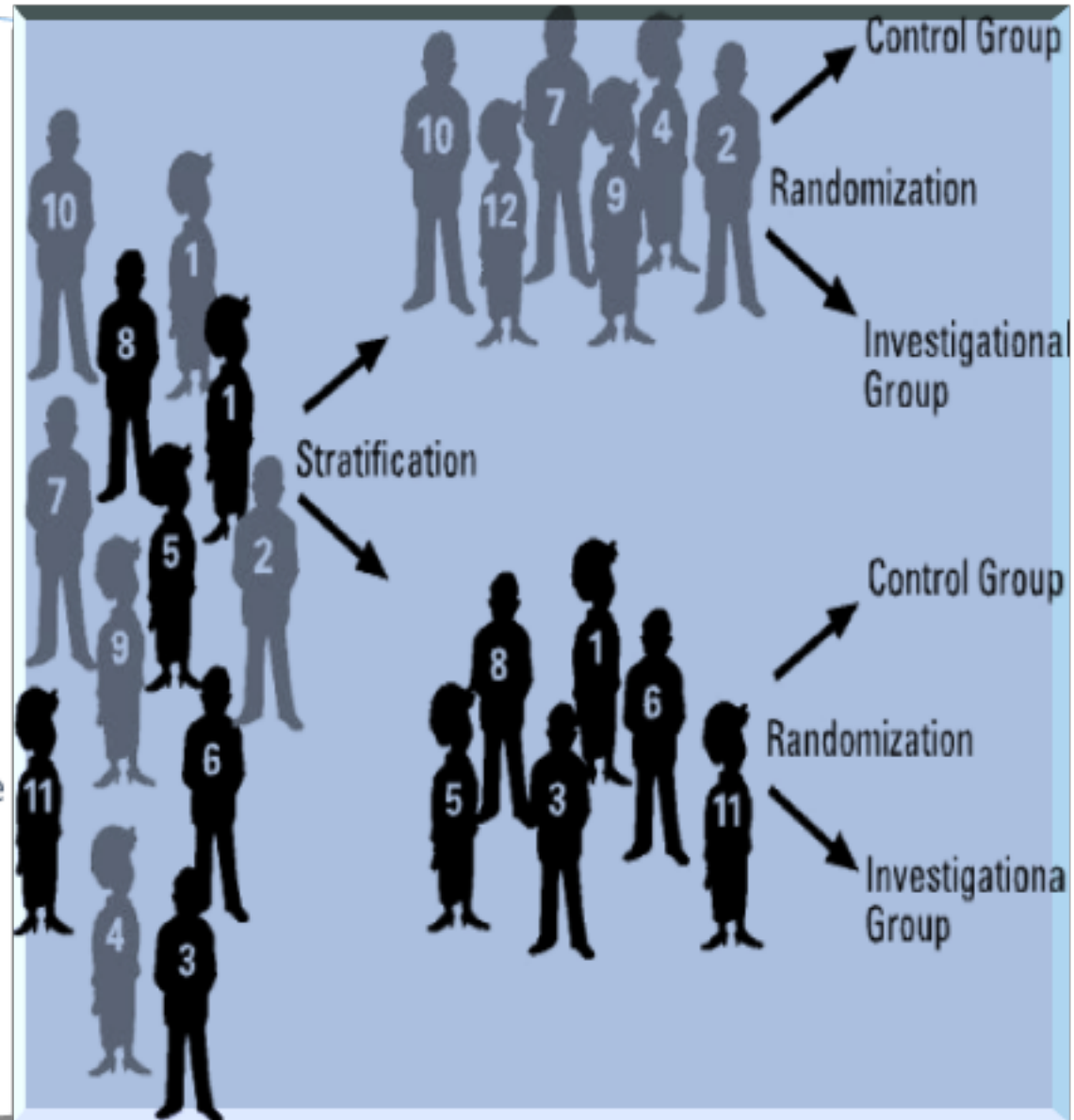
# Randomized Trials

- ❑ Participants have an equal chance to be assigned to one of two or more groups:
- ❑ One gets the most widely accepted treatment (standard treatment)
- ❑ The other gets the new treatment being tested, which researchers hope and have reason to believe will be better than standard treatment

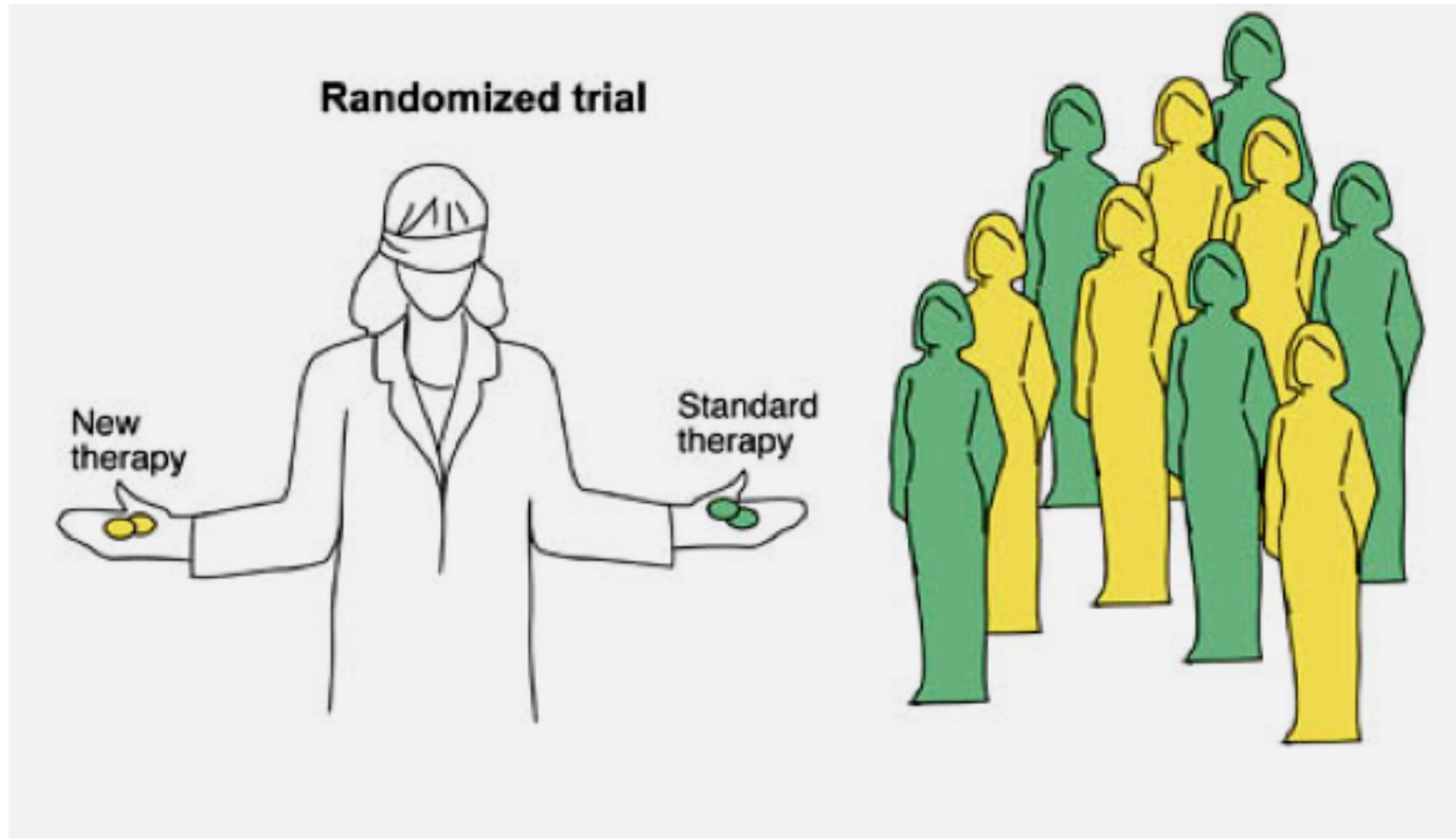


# Clinical Trial Design

- ❑ **Stratification:** Categorizing subjects into subgroups by specific characteristics
  - ❑ Enables researchers to look into separate subgroups to see whether differences exist
- ❑ Stratification is used in randomized trials when factors that can influence the intervention's success are known.
- ❑ For instance, participants whose cancer has spread from the original tumor site can be separated, or stratified, from those whose cancer has not spread.
- ❑ Assignment of interventions within the two groups is then randomized. Stratification enables researchers to look at factors in both groups.



# Double Blind Randomized Studies



**Considered the 'gold standard' since they control for bias and placebo effect**

# Placebo effects: Lab setting (experimental)

A placebo described as a **muscle relaxant** will cause muscle relaxation and, if described as the opposite, muscle tension.<sup>[40]</sup> A placebo presented as a **stimulant** will have this effect on **heart rhythm**, and **blood pressure**, but, when administered as a **depressant**, the opposite effect.<sup>[41]</sup> The perceived consumption of caffeine has been reported to cause similar effects even when decaffeinated coffee is consumed,<sup>[42] [43]</sup> although a 2003 study found only limited support for this.<sup>[44]</sup> Alcohol placebos can cause intoxication<sup>[45]</sup> and sensorimotor impairment.<sup>[46]</sup> Perceived **ergogenic aids** can increase endurance,<sup>[47]</sup> speed<sup>[48]</sup> and weight-lifting ability,<sup>[49]</sup> leading to the question of whether placebos should be allowed in sport competition.<sup>[50]</sup> Placebos can help smokers quit.<sup>[51]</sup> Perceived allergens that are not truly allergenic can cause allergies.<sup>[52]</sup> Interventions such as psychotherapy can have placebo effects.<sup>[53]</sup> pp 164–173 The effect has been observed in the **transplantation of human embryonic neurons** into the brains of those with advanced **Parkinson's disease**.<sup>[54]</sup>

**Injection or pill color preferences differ geographically, ethnically**

**Antidepressant drugs**

**Works even if you know**

**Placebo effect is getting stronger *only in America* : new pain drugs work less well**

**“Real Life” Placebo effects**

**Antibiotics for “Flu”    regression to the mean    you were getting better**

**“Unintentional” large study – women who had been in placebo group for HRT began to experience hot flashes after being told to stop taken drug**



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ORIGINAL ARTICLE

## The Effect of Vitamin E and Beta Carotene on the Incidence of Lung Cancer and Other Cancers in Male Smokers

April 14, 1994 | The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group\*

Power Point Slide

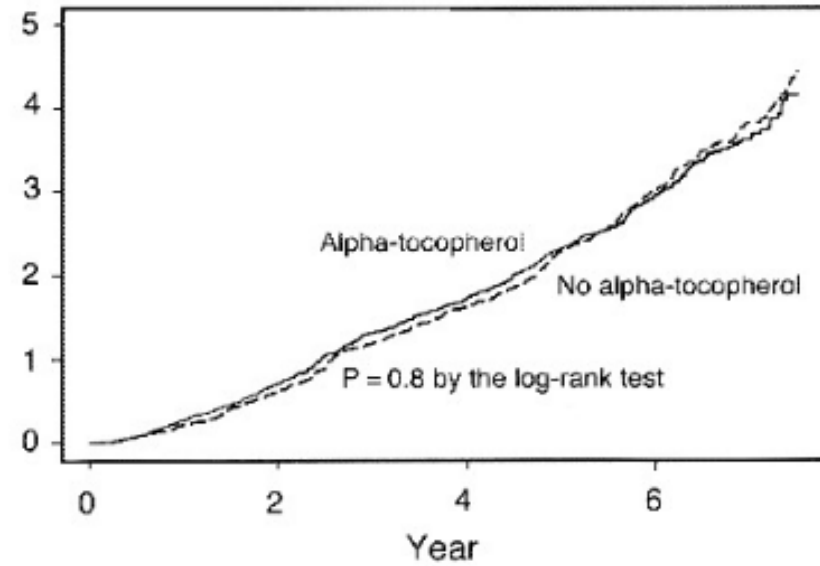
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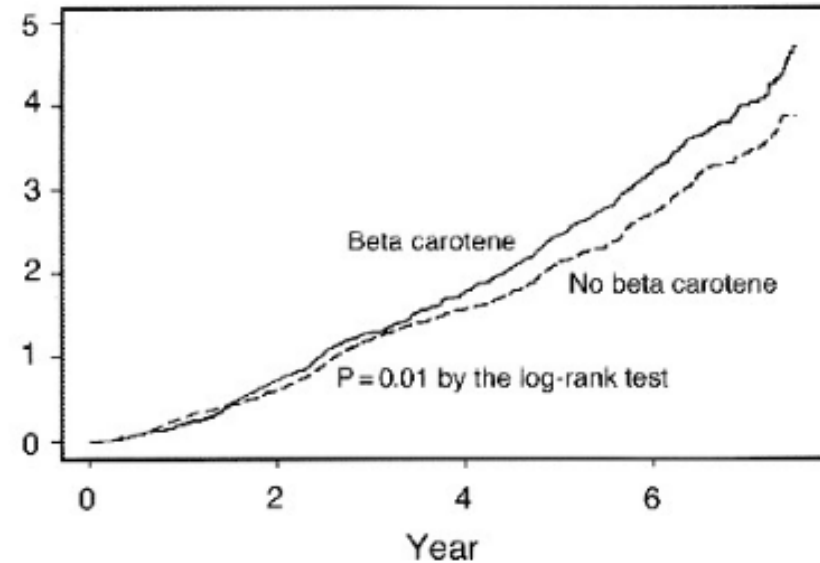
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Incidence of Lung Cancer (%)



Incidence of Lung Cancer (%)



# Hepatitis C (*Hep C*)

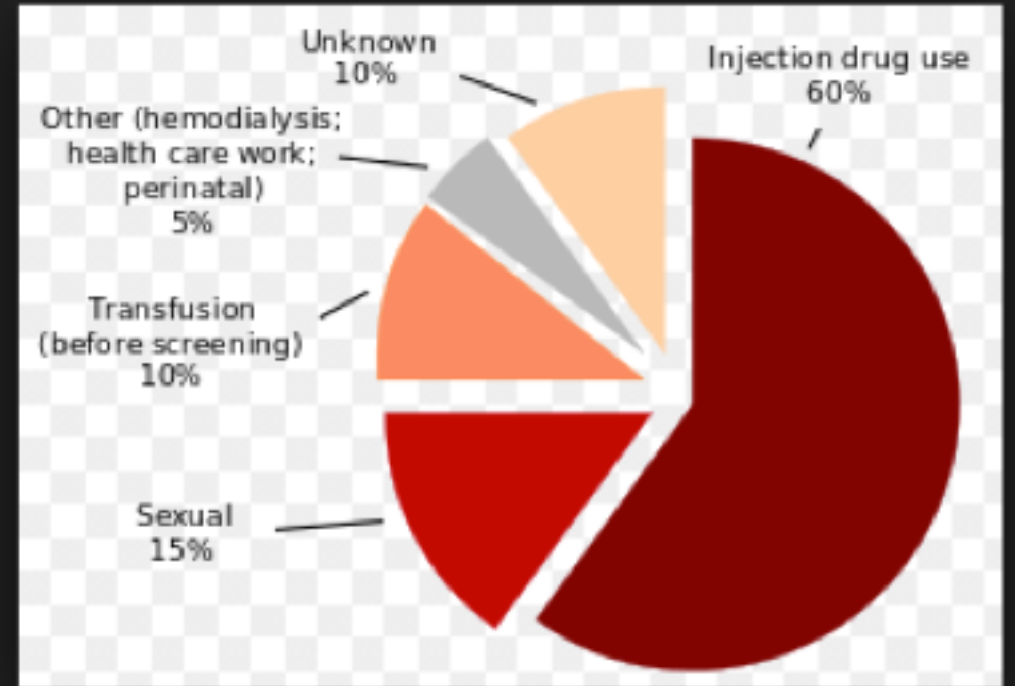
## “the forgotten virus”

150 million infected

500,000 deaths/yr

500,000 treated/yr

- 



310 × 215 - Images may be subject to copyright. [Learn More](#)

## The Deployment Problem Is Price



Source: Significant reductions in costs of generic production of sofosbuvir and daclatasvir for treatment of hepatitis C, Hill et al, EASL 2016 2

### Tallying the cost of hepatitis C



It costs **\$84,000** for treatment of hepatitis C on Gilead's Sovaldi, but the alternative, allowing the disease to progress, costs much more.

A liver transplant may cost about **\$200,000**, plus the patient will need anti-rejection medication, which can cost **\$40,000** a year, for the rest of their lives.

SOURCE: DR. DOUGLAS DIETERICH, MT. SINAI HOSPITAL

CNBC

## YOU MAY BE AT RISK IF YOU:



Many people can live with hepatitis C for years *without* symptoms. A blood test *is the only way* to know if you have been exposed to hepatitis C.



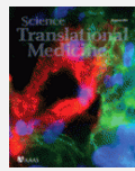
## Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Previous [research](#) on animal and physiological models suggests that antioxidant supplements have beneficial effects that may prolong life. Some observational studies also suggest that antioxidant supplements may prolong life, whereas other observational studies demonstrate neutral or harmful effects. Our Cochrane [review](#) from 2008 demonstrated that antioxidant supplements seem to increase [mortality](#). This [review](#) is now updated.

### Authors' conclusions:

We found no evidence to support antioxidant supplements for primary or secondary prevention. Beta-carotene and vitamin E seem to increase [mortality](#), and so may higher doses of vitamin A. Antioxidant supplements need to be considered as medicinal products and should undergo sufficient [evaluation](#) before marketing.

The present [systematic review](#) included 78 randomised clinical trials. In total, 296,707 participants were randomised to antioxidant supplements (beta-carotene, vitamin A, vitamin C, vitamin E, and selenium) versus [placebo](#) or no [intervention](#). Twenty-six trials included 215,900 healthy participants. Fifty-two trials included 80,807 participants with various diseases in a stable phase (including gastrointestinal, [cardiovascular](#), neurological, ocular, dermatological, [rheumatoid](#), renal, endocrinological, or unspecified diseases). A total of 21,484 of 183,749 participants (11.7%) randomised to antioxidant supplements and 11,479 of 112,958 participants (10.2%) randomised to [placebo](#) or no [intervention](#) died. The trials appeared to have enough statistical similarity that they could be combined. When all of the trials were combined, antioxidants may or may not have increased [mortality](#) depending on which statistical combination method was employed; the [analysis](#) that is typically used when similarity is present demonstrated that antioxidant use did slightly increase [mortality](#) (that is, the patients consuming the antioxidants were 1.03 times as likely to die as were the controls). When analyses were done to identify factors that were associated with this finding, the two factors identified were better methodology to prevent [bias](#) from being a factor in the [trial](#) (trials with 'low [risk](#) of bias') and the use of vitamin A. In fact, when the trials with low risks of [bias](#) were considered separately, the increased [mortality](#) was even more pronounced (1.04 times as likely to die as were the controls). The potential damage



# Antioxidants Accelerate Lung Cancer Progression in Mice

Volkan I. Sayin<sup>1,2,3</sup>, Mohamed X. Ibrahim<sup>1</sup>, Erik Larsson<sup>3</sup>, Jonas A. Nilsson<sup>1,4</sup>, Per Lindahl<sup>2,3,\*</sup> and Martin O. Bergo<sup>1,\*</sup>

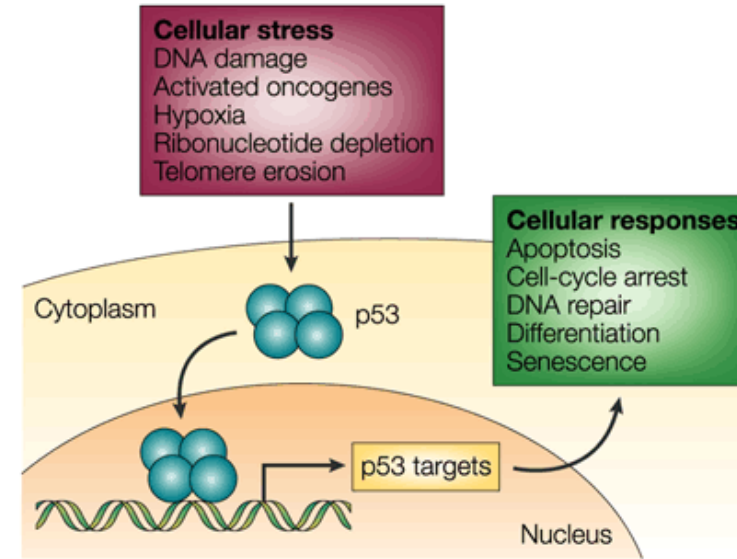
+ Author Affiliations

\*Corresponding author. E-mail: martin.bergo@gu.se (M.O.B.); per.lindahl@wlab.gu.se (P.L.)

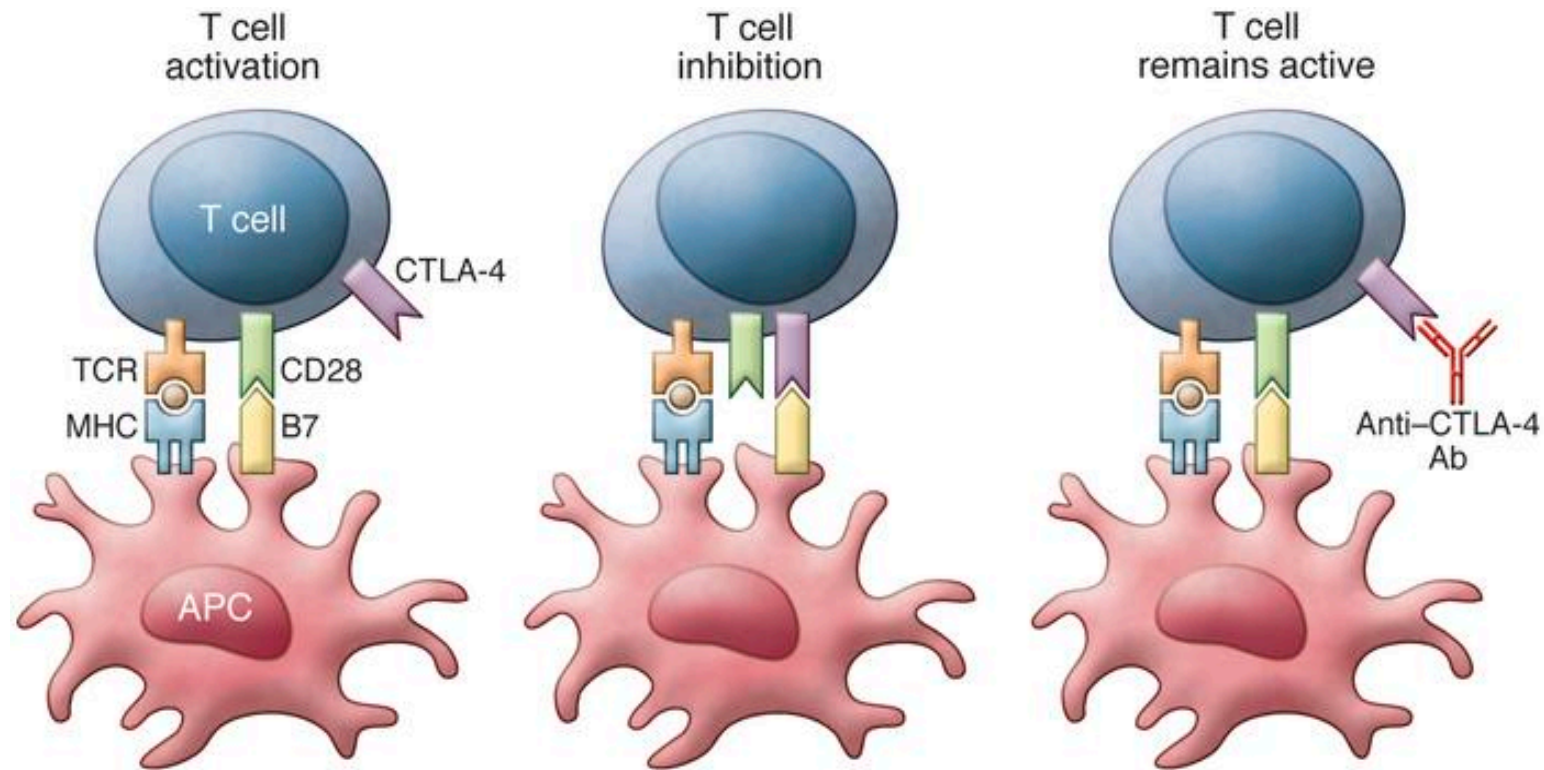
Science Translational Medicine 29 Jan 2014;  
Vol. 6, Issue 221, pp. 221ra15  
DOI: 10.1126/scitranslmed.3007653

## Abstract

Antioxidants are widely used to protect cells from damage induced by reactive oxygen species (ROS). The concept that antioxidants can help fight cancer is deeply rooted in the general population, promoted by the food supplement industry, and supported by some scientific studies. However, clinical trials have reported inconsistent results. We show that supplementing the diet with the antioxidants *N*-acetylcysteine (NAC) and vitamin E markedly increases tumor progression and reduces survival in mouse models of B-RAF- and K-RAS-induced lung cancer. RNA sequencing revealed that NAC and vitamin E, which are structurally unrelated, produce highly coordinated changes in tumor transcriptome profiles, dominated by reduced expression of endogenous antioxidant genes. NAC and vitamin E increase tumor cell proliferation by reducing ROS, DNA damage, and p53 expression in mouse and human lung tumor cells. Inactivation of p53 increases tumor growth to a similar degree as antioxidants and abolishes the antioxidant effect. Thus, antioxidants accelerate tumor growth by disrupting the ROS-p53 axis. Because somatic mutations in p53 occur late in tumor progression, antioxidants may accelerate the growth of early tumors or precancerous lesions in high-risk populations such as smokers and patients with chronic obstructive pulmonary disease who receive NAC to relieve mucus production.



**Figure 1: Cytotoxic T lymphocyte antigen-4 and immune checkpoint blockade**



## Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma.

Larkin J<sup>1</sup>, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD.

### ⊕ Author information

#### Abstract

**BACKGROUND:** Nivolumab (a programmed death 1 [PD-1] checkpoint inhibitor) and ipilimumab (a cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4] checkpoint inhibitor) have been shown to have complementary activity in metastatic melanoma. In this randomized, double-blind, phase 3 study, nivolumab alone or nivolumab plus ipilimumab was compared with ipilimumab alone in patients with metastatic melanoma.

**METHODS:** We assigned, in a 1:1:1 ratio, 945 previously untreated patients with unresectable stage III or IV melanoma to nivolumab alone, nivolumab plus ipilimumab, or ipilimumab alone. Progression-free survival and overall survival were coprimary end points. Results regarding progression-free survival are presented here.

**RESULTS:** The median progression-free survival was 11.5 months (95% confidence interval [CI], 8.9 to 16.7) with nivolumab plus ipilimumab, as compared with 2.9 months (95% CI, 2.8 to 3.4) with ipilimumab (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57;  $P < 0.001$ ), and 6.9 months (95% CI, 4.3 to 9.5) with nivolumab (hazard ratio for the comparison with ipilimumab, 0.57; 99.5% CI, 0.43 to 0.76;  $P < 0.001$ ). In patients with tumors positive for the PD-1 ligand (PD-L1), the median progression-free survival was 14.0 months in the nivolumab-plus-ipilimumab group and in the nivolumab group, but in patients with PD-L1-negative tumors, progression-free survival was longer with the combination therapy than with nivolumab alone (11.2 months [95% CI, 8.0 to not reached] vs. 5.3 months [95% CI, 2.8 to 7.1]). Treatment-related adverse events of grade 3 or 4 occurred in 16.3% of the patients in the nivolumab group, 55.0% of those in the nivolumab-plus-ipilimumab group, and 27.3% of those in the ipilimumab group.

**CONCLUSIONS:** Among previously untreated patients with metastatic melanoma, nivolumab alone or combined with ipilimumab resulted in significantly longer progression-free survival than ipilimumab alone. In patients with PD-L1-negative tumors, the combination of PD-1 and CTLA-4 blockade was more effective than either agent alone. (Funded by Bristol-Myers Squibb; CheckMate 067 ClinicalTrials.gov number, [NCT01844505](#).)

Combinatorial immunotherapy  
Adjuvant/neoadjuvant

# Not all supplements / Vitamins are useless

## Science-Based Medicine

About SBM " " Reference " "

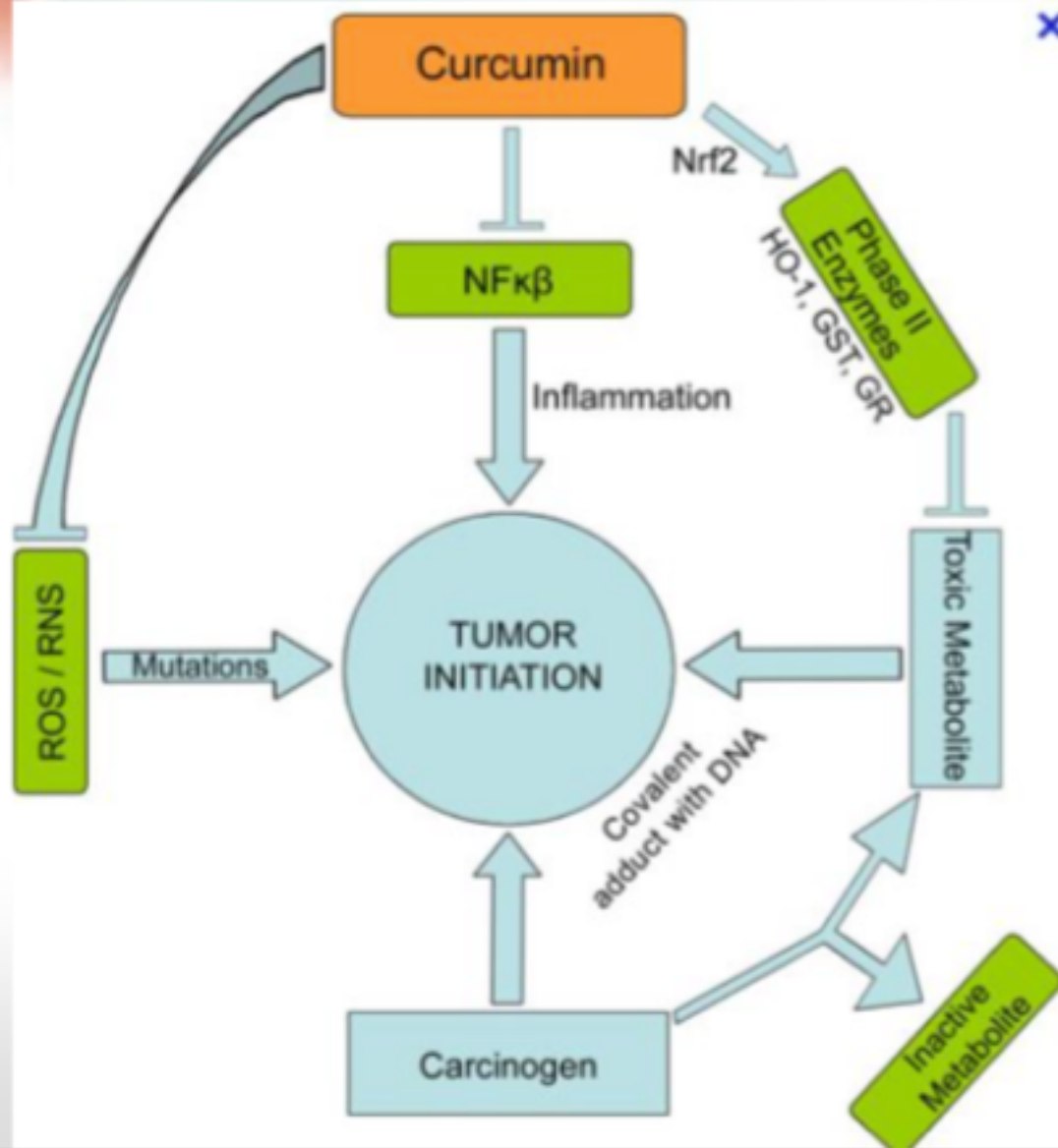
If scientific evidence guides our health decisions, we will look back at the vitamin craze of the last few decades with disbelief. Indiscriminate use is, in most cases, probably useless and potentially harmful. We are collectively throwing away billions of dollars into supplements, chasing the idea of benefits that have never materialized.

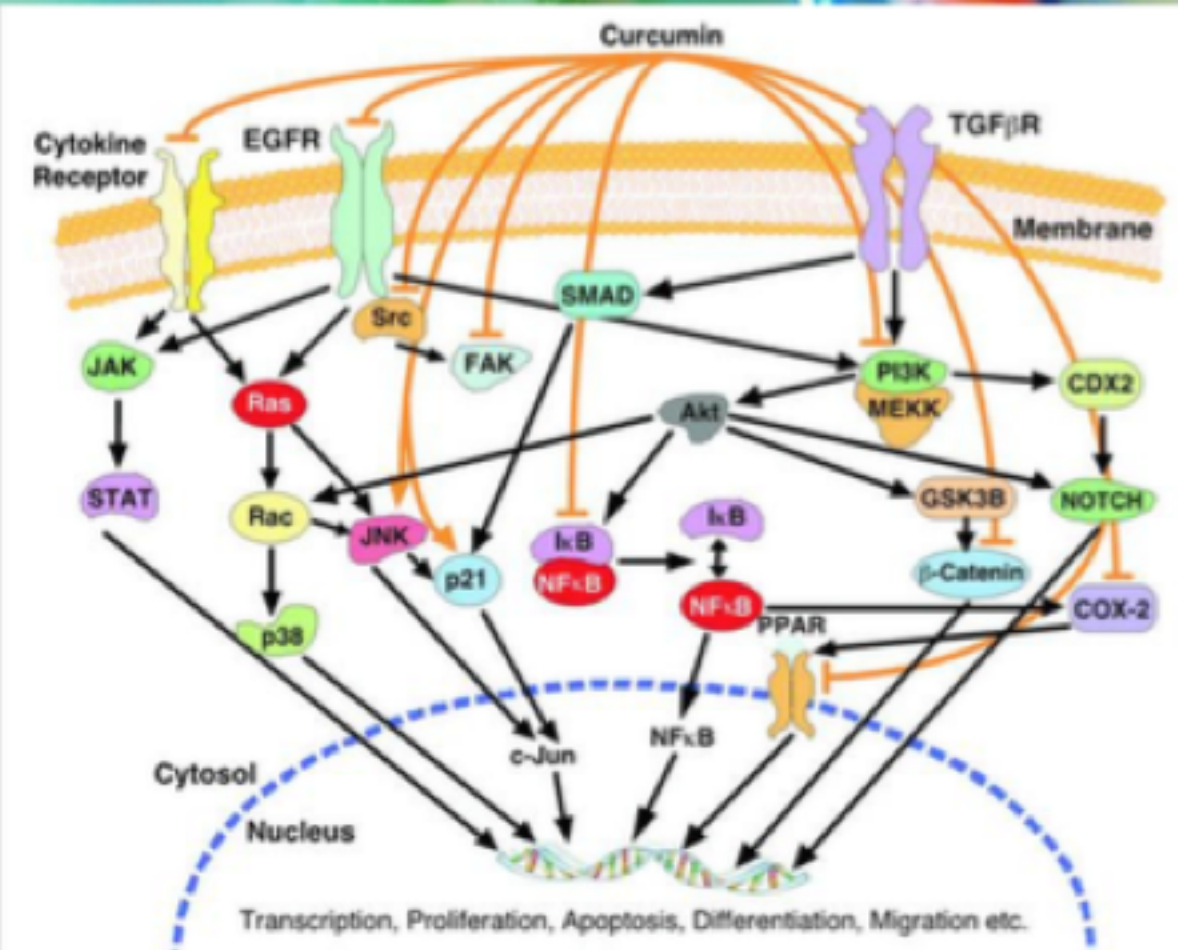
Multivitamins are marketed with a veneer of science but that image is a mirage – rigorous testing doesn't support the health claims. But I don't think the routine use of vitamins will disappear anytime soon. It's a skillfully-marketed panacea that about half of us buy into.

Not all vitamin and mineral supplementation is useless. They can be used appropriately, when our decisions are informed by scientific evidence: Folic acid prevents neural tube defects in the developing fetus. Vitamin B12 can reverse anemia. Vitamin D is recommended for breastfeeding babies to prevent deficiency. Vitamin K injections in newborns prevent potentially catastrophic bleeding events. But the most common reason for taking vitamins isn't a clear need, but rather our desire to "improve overall health". It's deemed "primary prevention" – the belief that we're just filling in the gaps in our diet. Others may believe that if vitamins are good, then more vitamins must be better. And there is no debate that we need dietary vitamins to live. The case for indiscriminate supplementation, however, has never been established. We've been led to believe, through very effective marketing, that taking vitamins is beneficial to our overall health – even if our health status is reasonably good. So if supplements truly provide real

- also calcium for bone loss

# Curcumin mechanism of action





- Traditional Indian medicine
- 5000 papers in PUBMED alone
- 1949 antimicrobial

# Curcumin as a Chemo preventative

Breaks down in 5 min in water  
Effective in combination?

## Journal of Medicinal Chemistry

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Perspective

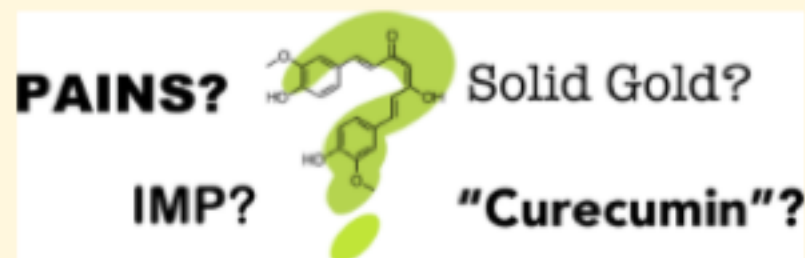
[pubs.acs.org/jmc](https://pubs.acs.org/jmc)

### The Essential Medicinal Chemistry of Curcumin

Miniperspective

Kathryn M. Nelson,<sup>†</sup> Jayme L. Dahlin,<sup>‡</sup> Jonathan Bisson,<sup>§</sup> James Graham,<sup>§</sup> Guido F. Pauli,<sup>§,||</sup> and Michael A. Walters<sup>\*,†</sup>

**ABSTRACT:** Curcumin is a constituent (up to ~5%) of the traditional medicine known as turmeric. Interest in the therapeutic use of turmeric and the relative ease of isolation of curcuminoids has led to their extensive investigation. Curcumin has recently been classified as both a PAINS (pan-assay interference compounds) and an IMPS (invalid metabolic panaceas) candidate. The likely false activity of curcumin in vitro and in vivo has resulted in >120 clinical trials of curcuminoids against several diseases. No double-blinded, placebo controlled clinical trial of curcumin has been successful. This manuscript reviews the essential medicinal chemistry of curcumin and provides evidence that curcumin is an unstable, reactive, nonbioavailable compound and, therefore, a highly improbable lead. On the basis of this in-depth evaluation, potential new directions for research on curcuminoids are discussed.

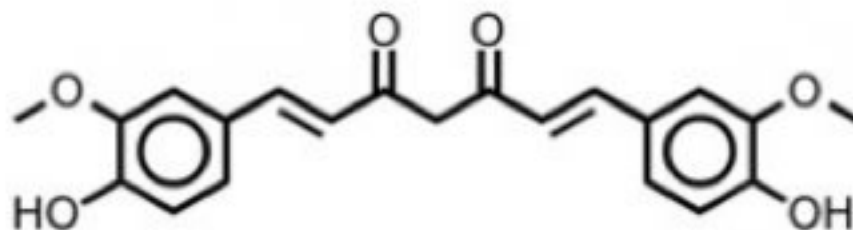


# Curcumin Will Waste Your Time

By [Derek Lowe](#) | 12 January, 2017

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I really enjoyed reading [this article](#) in J. Med. Chem. on [curcumin](#). (Update: [here's the take](#) over at *Practical Fragments*). That's a well-known natural product, found in large quantities in turmeric root (which is where most of the yellow color comes from). It has, over the years, been a hit in many, many assays, and I would not want to guess how many derivatives of the structure have been prepared along the way. There is an [entire web portal](#) that attempts to bring together all the publications (thousands) and patents (hundreds) relevant to the field. More than that, a quick search will reveal that there are plenty of people ready to sell you curcumin tablets in every variety, for a list of ailments longer than most people's legs. Everything from Alzheimer's to upset stomach – curcumin is good for what ails you, apparently.



LETTERS | 1 NOVEMBER 2016

## Do Sugar-Sweetened Beverages Cause Obesity and Diabetes? Industry and the Manufacture of Scientific Controversy

Dean Schillinger, MD; Jessica Tran, BA; Christina Mangurian, MD, MS; Cristin Kearns, DDS, MBA

[Article, Author, and Disclosure Information](#)

Play VIDEO

### Multiple cities look to decrease sugary drink intake

make them drink water -- actual experiments in humans over the last 15 years,” Schillinger said.

sugary beverages.

These are all “actual head-to-head comparison studies where you take people and you make them drink soda and you take other people and you

Out of 60 studies uncovered by the review, 26 received financial support from the beverage industry, the researchers found. Either the studies had been paid for by the beverage industry, or researchers participating in the study had financial ties to the industry.

None of the 26 industry-funded studies found a link between sugary drinks and obesity or diabetes, Schillinger said.

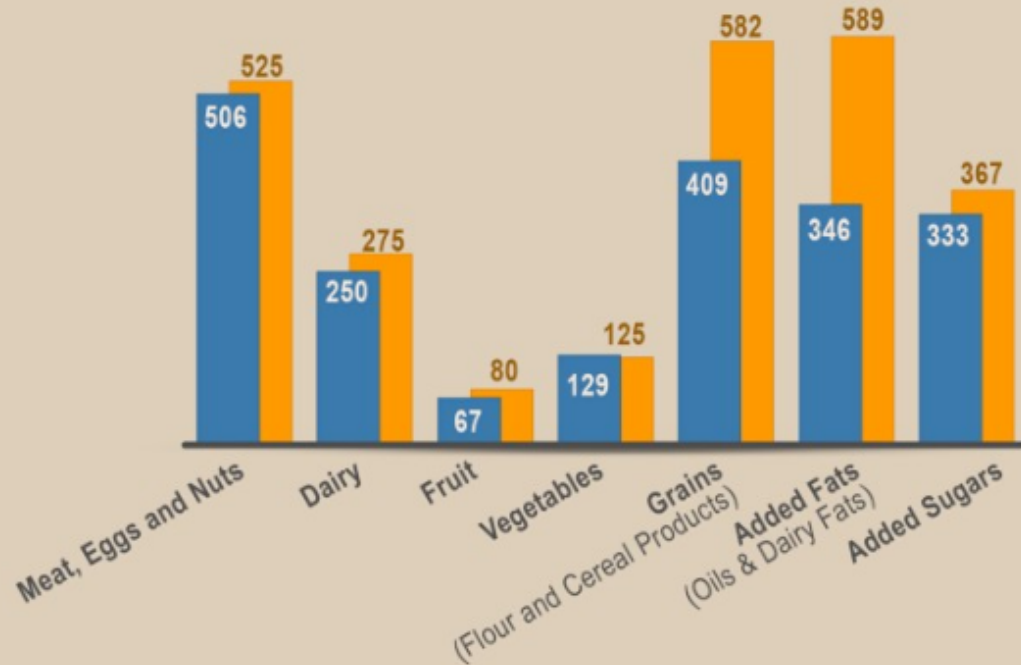
On the other hand, 33 out of 34 studies that reported a direct link between sugary drinks and obesity or diabetes had received no money from the beverage industry, the researchers said.

According to Dr. Michael Siegel, a professor of community health sciences with the Boston University School of Public Health, “It clearly reveals the bias that’s present in these studies. This is not a subtle finding.”

# Will soda/ sugar taxes lower obesity rates?

## DAILY CALORIES CONSUMED BY THE AVERAGE AMERICAN<sup>1</sup>

- Before the Obesity Crisis (Circa 1970)
- At the Peak of the Obesity Crisis (Circa 2010)



## IS JUNK FOOD TO BLAME FOR OBESITY IN THE U.S.?

OVERWEIGHT AND OBESITY RATES HAVE INCREASED SINCE THE 1970s BUT ARE THE COMMON CULPRITS FAST FOOD, SODA AND CANDY— ACTUALLY TO BLAME?

Total Daily Calories:



Soda and desserts are often blamed for high obesity rates because they are very calorie dense, while providing little nutrition. Such junk foods are high in added sugars. However, the bulk of the increase in calorie intake as obesity rates rose was from grains and fats.

<sup>1</sup> United States Department of Agriculture, Economic Research Service. (2013). Food Availability (Per Capita) Data Systems. Retrieved from [http://www.ers.usda.gov/data-products/food-availability-\(per-capita\)-data-system](http://www.ers.usda.gov/data-products/food-availability-(per-capita)-data-system)

# New study questions value of mammograms for breast cancer screening



## How it was done

Researchers used decades of federal surveys on mammography and cancer registry statistics to track how many **cancers were found when small** -- under 2 centimeters, or about three-fourths of an inch -- versus large, when they are presumably more life-threatening.

They estimated death rates according to the size of tumors for two periods -- 1975 through 1979, before mammograms were widely used, and a more recent period, 2000 through 2002.

In the earlier period, one-third of cancers found were small. In the later period, two-thirds were small. But the change was mostly because screening led to so many more cancers being detected overall, and the vast majority of them were small -- 162 more cases per 100,000 women, versus only 30 more cases of large tumors.

Assuming that the true number of cases of cancer in the population was stable, this implies that 132 cases per 100,000 women were overdiagnosed.

# Differences in Breast Cancer Mortality

Five-year estimates of breast cancer mortality rates (age-adjusted rate is per 100,000 females) for non-Hispanic black and non-Hispanic white women, 1990–2009\*

Black  
White

Baltimore, MD



Boston, MA



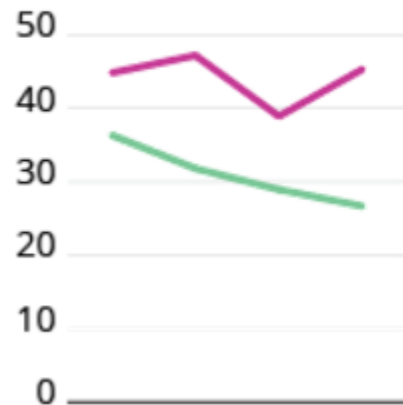
Chicago, IL



Cleveland, OH



Los Angeles, CA



Memphis, TN



- Nationally 40%
- LA 75%



# Triple-negative breast cancer in African-American women: disparities versus biology

## Abstract

[Abstract](#) • [References](#) • [Author information](#)

Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype that disproportionately affects *BRCA1* mutation carriers and young women of African origin. There is evidence that African-American women with TNBC have worse clinical outcomes than women of European descent. However, it is unclear whether survival differences persist after adjusting for disparities in access to health-care treatment, co-morbid disease and income. It remains controversial whether TNBC in African-American women is a molecularly distinct disease or whether African-American women have a higher incidence of aggressive biology driven by disparities: **there is evidence in support of both.** Understanding the relative contributions of biology and disparities is essential for improving the poor survival rate of African-American women with TNBC.

# BRCA risk is age dependent

Science. 2003 Oct 24;302(5645):643-6.

## **Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2.**

King MC<sup>1</sup>, Marks JH, Mandell JB; New York Breast Cancer Study Group.

### **Author information**

### **Abstract**

Risks of breast and ovarian cancer were determined for Ashkenazi Jewish women with inherited mutations in the tumor suppressor genes BRCA1 and BRCA2. We selected 1008 index cases, regardless of family history of cancer, and carried out molecular analysis across entire families. The lifetime risk of breast cancer among female mutation carriers was 82%, similar to risks in families with many cases. Risks appear to be increasing with time: Breast cancer risk by age 50 among mutation carriers born before 1940 was 24%, but among those born after 1940 it was 67%. Lifetime risks of ovarian cancer were 54% for BRCA1 and 23% for BRCA2 mutation carriers. Physical exercise and lack of obesity in adolescence were associated with significantly delayed breast cancer onset.

## Reproductive factors and the risk of triple-negative breast cancer in white women and African-American women: a pooled analysis.

Ma H<sup>1</sup>, Ursin G<sup>2,3</sup>, Xu X<sup>4</sup>, Lee E<sup>5</sup>, Togawa K<sup>4,6</sup>, Duan L<sup>4,7</sup>, Lu Y<sup>4</sup>, Malone KE<sup>8</sup>, Marchbanks PA<sup>9</sup>, McDonald JA<sup>10</sup>, Simon MS<sup>11</sup>, Folger SG<sup>9</sup>, Sullivan-Halley J<sup>4</sup>, Deapen DM<sup>5</sup>, Press MF<sup>12</sup>, Bernstein L<sup>4</sup>.

### ⊕ Author information

#### Abstract

**BACKGROUND:** Early age at menarche, nulliparity, late age at first completed pregnancy, and never having breastfed, are established breast cancer risk factors. However, among breast cancer subtypes, it remains unclear whether all of these are risk factors for triple-negative breast cancer (TNBC).

**METHODS:** We evaluated the associations of these reproductive factors with TNBC, in 2658 patients with breast cancer (including 554 with TNBC) and 2448 controls aged 20-64 years, who participated in one of the three population-based case-control studies: the Women's Contraceptive and Reproductive Experiences Study, the Women's Breast Carcinoma in situ Study, or the Women's Learning the Influence of Family and Environment Study. We used multivariable polychotomous unconditional logistic regression methods to conduct case-control comparisons among breast cancer subtypes defined by estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 expression status.

**RESULTS:** TNBC risk decreased with increasing duration of breastfeeding ( $P_{\text{trend}} = 0.006$ ), but age at menarche, age at first completed pregnancy, and nulliparity were not associated with risk of TNBC. Parous women who breastfed for at least one year had a 31% lower risk of TNBC than parous women who had never breastfed (odds ratio, OR = 0.69; 95% confidence interval, CI = 0.50-0.96). The association between breastfeeding and risk of TNBC was modified by age and race. Parous African-American women aged 20-44 years who breastfed for 6 months or longer had an 82% lower risk of TNBC than their counterparts who had never breastfed (OR = 0.18, 95% CI = 0.07-0.46).

**CONCLUSIONS:** Our data indicate that breastfeeding decreases the risk of TNBC, especially for younger African-American women.

## Early onset breast cancer: differences in risk factors, tumor phenotype, and genotype between North African and South European women.

Corsini C<sup>1</sup>, Henouda S<sup>2</sup>, Nejima DB<sup>3</sup>, Bertet H<sup>4</sup>, Toledano A<sup>5</sup>, Boussen H<sup>6</sup>, Habib F<sup>7</sup>, Mouhout A<sup>7</sup>, Gaballah A<sup>8</sup>, Ghazaly HE<sup>8</sup>, Bourgier C<sup>9</sup>, Coupier J<sup>1</sup>, Galibert V<sup>1</sup>, Baudry K<sup>1</sup>, Vilquin P<sup>10</sup>, Biquard L<sup>11</sup>, Rey JM<sup>10</sup>, Belkacemi Y<sup>12</sup>, Ihout P<sup>5</sup>, Khayat D<sup>5</sup>, Picot MC<sup>4</sup>, Bensalem A<sup>13</sup>, Pujol P<sup>14,15</sup>.

### ⊕ Author information

#### Abstract

**PURPOSE:** This report compares the risk factors, the tumor phenotypes, and the BRCA1/BRCA2 genotype of early onset breast cancer (EOBC) patients between Southern Europe and North Africa.

**METHODS:** Four hundred and fifty six women with invasive EOBC (≤40 years) were prospectively included from four centers in France (n = 270) and four centers in North Africa (Algeria, Egypt, Morocco, Tunisia; n = 186). Life style, tumor phenotype, familial history, BRCA1/BRCA2 genotype were compared between the two populations.

**RESULTS:** We found an older age at menarche, a higher number of childbearing, a more frequent breastfeeding, a higher body mass index, a lower use of oral contraceptives in North African women compared to French women. TNM stage at diagnosis was higher in North African women than in French women. North African women had a lower incidence of triple negative and proliferative (Ki 67 index > 20%) tumors. There was a lower rate of BRCA1 mutation in North Africa (7 vs. 15%, P = 0.02). Three putative BRCA1/2 founder mutations were identified in North Africa.

**CONCLUSIONS:** In EOBC, we found significant differences in risk factors, phenotype and a higher incidence of BRCA1 mutations in Southern Europe as compared to North Africa. The worst prognosis previously reported for EOBC in North Africa is more likely due to a higher stage at diagnosis than to a more aggressive phenotype, since triple negative tumors are more common in Southern Europe and advanced tumors in North Africa.

# New Prostate Cancer Screening Rules Fail to Curb PSA Testing

By Rachael Rettner, Senior Writer | October 7, 2016 03:35pm ET



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Progress

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## Prostate Cancer: Screening

Release Date: May 2012



This topic is in the process of being updated. Please go to the [Update in Progress](#) section available.

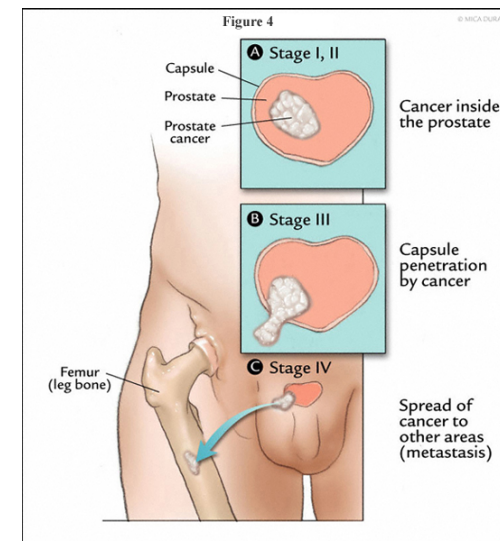
### Recommendation Summary

| Population              | Recommendation                                                                                                                           | Grade<br>(What's This?) |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| Men, Screening with PSA | The U.S. Preventive Services Task Force (USPSTF) recommends against prostate-specific antigen (PSA)-based screening for prostate cancer. | <b>D</b>                |

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# PSA Testing misleading biomarker?



# E cigarette Safety

*Prev Med.* 2014 Dec;69:248-60. doi: 10.1016/j.ypmed.2014.10.009. Epub 2014 Oct 16.

## A systematic review of health effects of electronic cigarettes.

*Pisinger C*<sup>1</sup>, *Døssing M*<sup>2</sup>.

### ⊕ Author information

#### Abstract

**OBJECTIVE:** To provide a systematic review of the existing literature on health consequences of vaping of electronic cigarettes (ECs).

**METHODS:** Search in: PubMed, EMBASE and CINAHL.

**INCLUSION CRITERIA:** Original publications describing a health-related topic, published before 14 August 2014. PRISMA recommendations were followed. We identified 1101 studies; 271 relevant after screening; 94 eligible.

**RESULTS:** We included 76 studies investigating content of fluid/vapor of ECs, reports on adverse events and human and animal experimental studies. Serious methodological problems were identified. In 34% of the articles the authors had a conflict of interest. Studies found fine/ultrafine particles, harmful metals, carcinogenic tobacco-specific nitrosamines, volatile organic compounds, carcinogenic carbonyls (some in high but most in low/trace concentrations), cytotoxicity and changed gene expression. Of special concern are compounds not found in conventional cigarettes, e.g. propylene glycol. Experimental studies found increased airway resistance after short-term exposure. Reports on short-term adverse events were often flawed by selection bias.

**CONCLUSIONS:** Due to many methodological problems, severe conflicts of interest, the relatively few and often small studies, the inconsistencies and contradictions in results, and the lack of long-term follow-up no firm conclusions can be drawn on the safety of ECs. However, they can hardly be considered harmless.

## Tobacco Products

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### Products, Ingredients & Components

## Vaporizers, E-Cigarettes, and other Electronic Nicotine Delivery Systems (ENDS)

### Statistics about ENDS Use

- More than 3 million middle and high school students were current users of e-cigarettes in 2015, up from an estimated 2.46 million in 2014.<sup>1,2</sup>
- Sixteen percent of high school and 5.3 percent of middle school students were current users of e-cigarettes in 2015, making e-cigarettes the most commonly used tobacco product among youth for the second consecutive year.<sup>1</sup>
- During 2011-2015, e-cigarette use rose from 1.5 percent to 16.0 percent among high school students and from 0.6 percent to 5.3 percent among middle school students.<sup>1</sup>
- In 2013-2014, 81% of current youth e-cigarette users cited the availability of appealing flavors as the primary reason for use.<sup>3</sup>
- In 2014, 12.6% of U.S. adults had ever tried an e-cigarette, and about 3.7% of adults used e-cigarettes daily or some days.<sup>4</sup>

### FDA Regulation of ENDS

In 2016, FDA finalized a rule extending our regulatory authority to cover all tobacco products, including vaporizers, vape pens, hookah pens, electronic cigarettes (E-Cigarettes), e-pipes, and all other ENDS. FDA now regulates the manufacture, import, packaging, labeling, advertising, promotion, sale, and distribution of ENDS. This includes components and parts of ENDS\* but excludes accessories.