‘Epigenetic’
NUTRITIONAL GENOMICS
ve Zeytinyag

Ankara Rotary
‘Epigenetic’

NUTRITIONAL GENOMICS

ve Zeytinyağ

Dr. Yahya Laleli
Düzen Laboratuvarlar Grubu
New York'ta Hunter Üniversitesi'nden bilim adamlarının fareler üzerinde yaptığı araştırma, zeytinyağında acımsı tat veren bu antioksidan maddenin kanser hücrelerinin içine girerek "hücrenin midesi" olarak nitelendirilen lizozomları, dolayısıyla kanseri 1 saatten kısa sürede yok edebileceğini gösterdi.

Maddenin prostat, meme ve pankreas kanserleri üzerinde etkili olduğunu belirten bilim adamları, kanserle mücadele için 90 kilo ağırlığındaki bir kişinin en az 2,25 litre zeytinyağı tüketmesi gerektiğini örneğini verdi.

Oleokantalın her gün tüketildiğinde etkili olabileceği ifade eden bilim adamlarından Paul Breslin, sonuçların kesinlik kazanması için hayvanlar ve insanlar üzerinde daha fazla çalışmaya ihtiyaç duyuldığuna da dikkati çekti.
Zeytinyağı, kanser hücrelerini 1 saatte yok ediyor
ABD'de yapılan bir araştırma, zeytinyağındaki oleokantal maddesinin kanser hücrelerini 1 saatten kısa sürede yok edebileceğini gösterdi.

Günlük Gazeteler ve Sosyal Medya üzerinde 142 adet haber yapılmıştır.
(-)-Oleocanthal rapidly and selectively induces cancer cell death via lysosomal membrane permeabilization (LMP)

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Accepted author version posted online: 23 Jan 2015.

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(-)-Oleocanthal rapidly and selectively induces cancer cell death via lysosomal membrane permeabilization (LMP)

O LeGendre$^{1,2}$, PAS Breslin$^{3,4}$, and DA Foster$^1$*

Abstract

(-)-Oleocanthal (OC), a phenolic compound in extra virgin olive oil (EVOO), has been implicated in the health benefits associated with diets rich in EVOO. We investigated the effect of OC on human cancer cell lines in culture. Amazingly, OC induced cell death in all cancer cells examined – as rapidly as 30 minutes after treatment in the absence of serum. OC treatment of non-transformed cells suppressed proliferation, but did not cause cell death. OC induced both primary necrotic and apoptotic cell death via induction of lysosomal membrane permeabilization (LMP). We provide evidence that OC promotes LMP by inhibiting acid sphingomyelinase (ASM) activity, which destabilizes the interaction between proteins necessary for lysosomal membrane stability.
What is Epigenetic

Epigenetics is the study of cellular and physiological traits that are heritable by daughter cells and not caused by changes in the DNA sequence; epigenetics describes the study of stable, long-term alterations in the transcriptional potential of a cell. These alterations may or may not be heritable. Examples of mechanisms that produce such changes are DNA methylation and histone modification, each of which alters how genes are expressed without altering the underlying DNA sequence.
Methylation of DNA

http://learn.genetics.utah.edu/content/epigenetics/nuhttp
Diets & Phenotype

These Two Mice are Genetically Identical and the Same Age

While pregnant, both of their mothers were fed Bisphenol A (BPA) but DIFFERENT DIETS:

- The mother of this mouse received a normal mouse diet
- The mother of this mouse received a diet supplemented with choline, folic acid, betaine and vitamin B12

http://learn.genetics.utah.edu/content/epigenetics/nuhttp
The Epigenomics of Cancer

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DOI 10.1016/j.cell.2007.01.029

Aberrant gene function and altered patterns of gene expression are key features of cancer. Growing evidence shows that acquired epigenetic abnormalities participate with genetic alterations to cause this dysregulation. Here, we review recent advances in understanding how epigenetic alterations participate in the earliest stages of neoplasia, including stem/precursor cell contributions, and discuss the growing implications of these advances for strategies to control cancer.

For decades, scientists have been engaged in dissecting the origins of human cancer, and the relative roles of genetic versus epigenetic abnormalities have been hotly debated. An explosion of data indicating the importance of epigenetic processes, especially those resulting in the silencing of key regulatory genes, has led to the realization that genetics and epigenetics cooperate at all stages of cancer development. Recent advances include the understanding that silencing is part of global epigenomic alterations in cancer, that pathways relevant to stem cell growth and differentiation become altered, and the approval of three drugs that target these defects in cancer patients.

It must be appreciated, as we will outline, that epigenetic abnormalities in cancer comprise a multitude of aberrations in virtually every component of chromatin involved in packaging the human genome. Since epigenetic silencing processes are mitotically heritable, they can play the same roles and undergo the same selective processes as genetic alterations in the development of a cancer. A principal tenet of Darwin’s hypotheses for the evolution of species is that most germline mutations are deleterious, or of no functional significance; mutations give rise to a specific advantage selected for in an evolving population. These same selective concepts apply for epigenetic events, which can occur at a much more increased rate compared to mutations in somatic cells. Alterations in
1. Aberrant gene function and altered patterns of gene expression are key features of cancer.
2. Acquired epigenetic abnormalities participate with genetic alterations to cause this dysregulation.
3. How epigenetic alterations participate in the earliest stages of neoplasia.
4. An explosion of data has led to the realization
5. That genetics and epigenetics cooperate at all stages of cancer development.
6. Epigenetic changes can collaborate with genetic changes to cause the evolution of a cancer because they are mitotically heritable.
Adherence to a Mediterranean Diet and Survival in a Greek Population

Antonia Trichopoulou, M.D., Tina Costacou, Ph.D., Christina Bamia, Ph.D., and Dimitrios Trichopoulou, M.D. population-based, prospective investigation involving 22,043 adults in Greece.

Adherence to the traditional Mediterranean diet was assessed by a 10-point Mediterranean-proportional hazards adjustment for age, sex, body-mass index, physical-activity level, and other potential confounders regression to assess the relation between adherence to the Mediterranean diet and total mortality, as well as mortality due to coronary heart disease and mortality due to cancer, with.

During a median of 44 months of follow-up, there were 275 deaths. A higher degree of adherence to the Mediterranean diet was associated with a reduction in total mortality.
Scientific evidence of the benefits of virgin olive oil for human health

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Olive oil is considered to be one of the most healthy dietary fats. There are, however, several types of olive oil present on the market. With the data at present available, the most healthy of them is the virgin olive oil (VOO), rich in phenolic compounds.

On November 2011, the European Food Safety Authority (EFSA) released a claim concerning the benefits of the daily ingestion of olive oil rich in phenolic compounds, such as the VOO. In this review, we will summarize the work which have provided scientific evidence of the benefits of VOO consumption over other type of edible oils even olive oils. Data from randomized, controlled human studies, will be presented. This type of studies are able to provide evidence of Level I which is that required for performing nutritional recommendations.
Limited and not conclusive scientific evidence suggests that eating about 2 tablespoons (23 grams) of olive oil daily may reduce the risk of coronary heart disease due to the monounsaturated fat in olive oil.

To achieve this possible benefit, olive oil is to replace a similar amount of saturated fat and not increase the total number of calories you eat in a day.
Diet modifications:
• Maintaining healthiness
• Preventing disease onset
• Delaying disease onset

Nutritional Genomics:
• Relate the genetic composition with diet
• Provide means to develop molecular markers for
  • Protective effect
  • Disease follow-up
DIET AND GENE EXPRESSION

(A) Direct relation between the nutrients and gene expression
(B) and (C) Indirect relation between the nutrients and gene expression

http://nutrigenomics.ucdavis.edu/?page=Information/Concepts_in_Nutrigenomics/Diet_and_Gene_Expression
On the properties of food, Galenos stated in the 2nd century that

1st Theory: “Excretions of Body Fluids”

The main aim of a physician-nutritionist or the one who prescribe his own formula is to balance the excretion of body fluids and to maintain this balance. This person should diagnose the internals of a person appropriately and should know the nutritional values of the food.

2nd Theory: “Power of the Foods”

If “the power” of each nutrient is known, then appropriate foods and drinks can be prescribed for adequate nutrition as well as maintaining ideal balance for excretion of body fluids.
A. cancer cell

CYP1B1

Salvestrol

activated Salvestrol metabolite destroys cancer cell

B. normal cell

no harm comes to normal cell
"Inhibits the growth of HER2 cells and decreases the resistance against therapeutic drugs"*

*Menendez JA, et al. BMC Cancer 2007.
Olive Oil as a Naturally-Occurring “Anti-HER2 Cocktail”

In terms of protective effects against breast cancer, olive oil exhibits a “very favorable fat composition”

- a low $\omega$-6/$\omega$-3 PUFA ratio
- elevated $\omega$-9 MUFA levels

Menendez JA, et al. BMC Cancer 2007, 7:80
Epidemiological Studies
Baseline Characteristics by Categories of Modified Mediterranean Diet Score Among 74607 Participants in EPIC-elderly Study and 4047 Deaths

| Characteristic | Men |  | Men |  | Men |  | Women |  | Women |  | Women |  |
|---------------|-----|-----|-----|-----|-----|-----|-------|-----|-------|-----|-------|-----|
|               | Diet score 0-3 | Diet score 4-5 | Diet score 6-9 | Diet score 0-3 | Diet score 4-5 | Diet score 6-9 |
| Age           | No | Deaths (%) | No | Deaths (%) | No | Deaths (%) | No | Deaths (%) | No | Deaths (%) | No | Deaths (%) |
| 60-64         | 5763 | 443 | (7.7) | 6099 | 388 | (6.4) | 4105 | 169 | (4.1) | 11580 | 460 | (4.0) | 11784 | 361 | (3.1) | 7886 | 202 | (2.6) |
| 65-69         | 1624 | 183 | (11.3) | 1984 | 183 | (9.2) | 1833 | 101 | (5.5) | 4760 | 312 | (6.6) | 5151 | 265 | (5.1) | 3985 | 122 | (3.1) |
| 70-74         | 701 | 104 | (14.8) | 900 | 136 | (15.1) | 912 | 91 | (10.0) | 1249 | 116 | (9.3) | 1550 | 111 | (7.2) | 1303 | 59 | (4.5) |
| >75           | 97 | 32 | (33.0) | 217 | 62 | (28.6) | 310 | 47 | (15.2) | 166 | 29 | (17.5) | 311 | 36 | (11.6) | 337 | 35 | (10.4) |
| Smoking status | | | | | | | | | | | | | | | | |
| Never         | 2516 | 176 | (7.0) | 2920 | 162 | (5.5) | 2417 | 88 | (3.6) | 10292 | 386 | (3.8) | 12239 | 404 | (3.3) | 10253 | 270 | (2.6) |
| Former        | 3657 | 300 | (8.2) | 4653 | 387 | (8.3) | 3449 | 241 | (7.0) | 4097 | 235 | (5.7) | 4359 | 211 | (4.8) | 2305 | 99 | (4.3) |
| Current       | 2012 | 286 | (14.2) | 1627 | 220 | (13.5) | 1294 | 79 | (6.1) | 3366 | 296 | (8.8) | 2198 | 58 | (2.6) | 953 | 49 | (5.1) |
| Educational achievement | | | | | | | | | | | | | | | | |
| None or primary | 3828 | 416 | (10.9) | 3857 | 395 | (10.2) | 3922 | 217 | (5.5) | 8073 | 463 | (5.7) | 7785 | 340 | (4.4) | 6367 | 180 | (2.8) |
| Technical or professional | 2008 | 178 | (8.9) | 2177 | 174 | (8.0) | 1023 | 77 | (7.5) | 4835 | 253 | (5.2) | 3835 | 175 | (4.6) | 1327 | 58 | (4.4) |
| Secondary     | 581 | 46 | (7.9) | 944 | 69 | (7.3) | 947 | 41 | (4.3) | 2839 | 130 | (4.6) | 4217 | 145 | (3.4) | 3481 | 110 | (3.2) |
| University    | 1768 | 122 | 2222 | 131 | 1268 | 73 | 2008 | 77 | 2939 | 150 | 2336 | 70 | 1250 | 126 | 1100 | 90 | 2005 | 51 | 1149 | 39 |
Association Between Mediterranean-Style Diet and Myocardial Infarction in USA (n=2568 / av. 9 years of follow-up)

| Mediterranean Diet Score | Model 1                  | Model 2                  |
|--------------------------|--------------------------|--------------------------|
| 0-2 (n=348)              | 1.00 (reference)         | 1.00 (reference)         |
| 3 (n=437)                | 0.55 (0.31, 1.00)        | 0.57 (0.32, 1.03)        |
| 4 (n=576)                | 0.62 (0.36, 1.06)        | 0.62 (0.37, 1.06)        |
| 5 (n=572)                | 0.59 (0.34, 1.03)        | 0.60 (0.34, 1.04)        |
| 6-9 (n=635)              | 0.61 (0.35, 1.04)        | 0.65 (0.38, 1.12)        |

P-trend

| Continuous: 1-point increase | Model 1                  | Model 2                  |
|------------------------------|--------------------------|--------------------------|
|                              | 0.93 (0.83, 1.04)        | 0.94 (0.84, 1.05)        |

- All values are HRs for combined vascular events; 95% CIs in parentheses. Calculated by using Cox proportional hazards models.
- Model 1 controlled for age at baseline, sex, race-ethnicity, completion of high school education, moderate-to-heavy physical activity, kilocalories, and cigarette smoking.
- Model 2 controlled for hypertension, diabetes, hypercholesterolemia, and history of cardiac disease in addition to Model 1.

Gardener H, et al. Am J Clin Nutr. 2011;94(6):1458-64.
### Association Between Mediterranean-Style Diet and Vascular Death in USA (n=2568 / av. 9 years of follow-up)

Vascular death (n = 314)

| Mediterranean Diet Score | Model 1                  | Model 2                  |
|--------------------------|--------------------------|--------------------------|
| 0-2 (n=348)              | 1.00 (reference)         | 1.00 (reference)         |
| 3 (n=437)                | 0.90 (0.62, 1.29)        | 0.87 (0.60, 1.26)        |
| 4 (n=576)                | 0.76 (0.53, 1.09)        | 0.74 (0.52, 1.06)        |
| 5 (n=572)                | 0.70 (0.48, 1.02)        | 0.69 (0.47, 1.00)        |
| 6-9 (n=635)              | 0.67 (0.46, 0.98)        | 0.71 (0.49, 1.04)        |
| P-trend                  | 0.02                     | 0.04                     |

### Continuous: 1-point increase

|                      | Model 1                  | Model 2                  |
|----------------------|--------------------------|--------------------------|
|                      | 0.91 (0.84, 0.97)        | 0.91 (0.85, 0.98)        |

- All values are HRs for combined vascular events; 95% CIs in parentheses. Calculated by using Cox proportional hazards models.
- Model 1 controlled for age at baseline, sex, race-ethnicity, completion of high school education, moderate-to-heavy physical activity, kilocalories, and cigarette smoking.
- Model 2 controlled for hypertension, diabetes, hypercholesterolemia, and history of cardiac disease in addition to Model 1.

Gardener H, et al. Am J Clin Nutr. 2011;94(6):1458-64.
Mediterranean Diet Can Reverse Metabolic Syndrome

By CHRIS LINDAHL on October 14, 2014
Filed in Health | No Comments Yet

5,801 people aged 55-80 were put on a Mediterranean diet that included olive oil and nuts, or a low-fat diet.

A study published this week shows that following a Mediterranean diet may help reverse metabolic syndrome, a condition that affects up to 25 percent of adults.

At the beginning of the study 64 percent of the participants had metabolic syndrome.

After 5 years, 28.2 percent of those on the Mediterranean diet no longer met the criteria for the condition.

These results support a long history of findings that sticking to a traditional diet found in the Mediterranean can support cardiovascular health.

The Spanish government-funded study was published today in the Canadian Medical Association Journal. Research led by Dr. Jordi Salas-Salvado, professor of nutrition at the Universitat Rovira i Virgili found that while following a Mediterranean diet did not lower the odds of developing the syndrome, it did lead to a significant probability of reversal.
Ingredients of Olive Oil

**Saponified, Glyceride Fraction**
(Triacylglycerol)
Mono unsaturated, poly unsaturated (essential) and saturated fatty acids

- Oleic acid
- Linoleic acid
- Linolenic acid
- Palmitic acid
- Stearic acid

**Sterols**
- Beta-Sitosterol
- 5-Anemosterol
- Campesterol
- Estigmasterol
- $\Delta^7$-Estigmasterol
- $\Delta^5$-Avenasterol
- $\Delta^7$-Avenasterol

**Alcohols**
- Aliphatic and triterpene alcohols

**Polyphenols**
- Lipophilic phenolics (Vitamin E, Alpha tocopherol)
- Hydrophilic phenolics (Hydroxytyrosol, Tyrosol, etc.)
- Secoiridoids (oleuropein and its aglycone derivative)
- Lignans

**Hydrocarbons**
- Squalene
- $\beta$-Carotene
- Lycopene

**Aromatic Compounds**
- Aldehydes: Acid aldehyde propanol, 2 and 3 sis and trans-hexenals
- Ketones: Pentan-3-on, 1-penton–3-on-1-octan-3-on
- Alcohol: Ethanol, Pentan, Hexane, Methylpropane, Methylbutane, etc.
- Acids: Acetic acid, Propanoic acid, 2-3 Methyl Butyric acid, etc.

**Pigments**
- Chlorophyll (a and b) and degradation product Pheophitins

**Unsaponified, Non-Glyceride Fraction**
Healthy Effects of Extra Virgin Olive Oil Compounds

Inflammation

- Oxidation and oxidative stress

Obesity and Diabetes

- Neoplasm

- Increase in the sense of satiety

Neoplasm

- Carotenoids

- Tocopherols

- Fatty acids

- Oleic acid

- α-linolenic acid

- Hydroxyl-oleic acid

Arterial hypertension

- Hypercholesterolaemia, serum lipoprotein levels and atherosclerosis

Phenolic compounds

- Tyrosol

- Hydroxytyrosol

- Oleocanthal

- Oleuropein

Oleocanthal

Oleuropein

Compounds

Caramia et al. Eur. J. Lipid Sci. Technol. 2012, 114:977-89.
Under normal conditions in a yeast cell, the longevity protein Sir2 uses NAD as a cofactor to produce nicotinamide, which then inhibits Sir2 in a negative feedback loop. But when the cell is exposed to environmental stresses like calorie restriction, heat shock, or osmotic stress (top), PNC1 gets switched on. The Pnc1 protein converts nicotinamide to nicotinic acid, a molecule that has no effect on Sir2. No longer inhibited by nicotinamide, Sir2 becomes more active and yeast live longer.
Olive oil and red wine antioxidant polyphenols at nutritionally relevant concentrations transcriptionally inhibit endothelial adhesion molecule expression, thus partially explaining atheroprotection from Mediterranean diets.

Carluccio MA, et al. Arterioscler Thromb Vasc Biol 2003, 23:622-9.
How International Taste and Quality Assessments are performed?

1) Chemical Analysis (by an accredited laboratory)
   a) Acidity of oil
   b) Peroxide value
   c) UV absorptivity
   d) Fatty acid profile

2) Sensory Analysis (by certified tasters)
   *Positive Attributes  *Negative Attributes (that shouldn’t be in the oil)
   a) Impression  Taste: humid-metallic-woody-earthy-sour-vinegary-fusty
   b) Appearance
   c) Odor
   d) Bitterness (on tongue)
   e) Pungency (on throat)
   f) Taste (fruity-almond-green leaf-unripe banana)
Four tastes recognized by the tongue, namely bitter, sweet, salt, and sour. Since olive oil does not contain any sugary substances, any sweet taste is due to the lack of required bitterness.

Nose and pharynx sense the various aroma. Taste and odor is intertwined into each other. The favored fruity taste can be sensed most prominently during the first time of smelling, which is the most delicate sense.

Color of the oil affects the judgment of the taster. Therefore, it is hidden by using colored glasses to avoid bias.

For Sensory Analysis...
WHAT KIND OF OLIVE OIL?

OLIVE OIL STANDARD-A

- Acidity
- Peroxide level
- UV absorptivity
- Fatty acid profile
- Pyropheophytin a
- Diacylglycerol (DAG)
- Polycyclic aromatic hydrocarbons (PAHs)

All of them, except DAG, is used to prevent low quality

Turkish Food Codex - Olive Oil and Bagasse Oil Notification (Date and Number: 20.11.2014/53)
WHAT KIND OF OLIVE OIL?

Level of organoleptic characters in the olive oil depends on:

- Region that the olive trees are grown
- Seasonal conditions
- Harvesting time & condition
- Processing techniques
- Storage conditions
- Bottling method

![Graph showing Fruit Polyphenol Level & Color during the Growing Season](image-url)
For a Healthy Life, At All Stages of Life, For Everyone

• Pregnancy
• Infancy
• Childhood
• Adolescence
• Adulthood
• Elderly

Olive Oil with High Organoleptic Characters, WITHOUT GAINING WEIGHT