

BREAST WELLNESS
A FUNCTIONAL APPROACH TO
CANCER

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FUNCTIONAL MEDICINE

- Prevention
- Underlying Causes
- Science Based
- Biochemical Individuality
- Patient Centered (Not Disease Centered)
- Interconnections in our body
 - Inflammation and heart disease
 - Gut and immune system

ASKS WHY???

Not just breast cancer.....

but breast cancers

Create A Healthy Terrain

Remove What Causes Imbalance

Replace What Is Needed For Balance



ESTROGEN

- As estrogen exposure increases so does our risk of breast cancer
 - Number of periods in your lifetime
 - BCPs >5 years or current use
 - HRT - 8.6% decrease in postmenopausal ER+ breast cancer since 2001
 - Endocrine Disrupters





Endocrine Disruptors -

Substances that mimic or disturb the activity or binding of our hormones

- Xenoestrogen - synthetic chemicals that act as endocrine disruptors
- Plastics -
 - BPA - Bisphenol A - #7
 - PVC - Polyvinyl chloride - phthalates
- Pesticides
carcinogens and endocrine disruptors



What can you do?

- Buy organic
 - Decreased pesticide exposure
 - Decreased growth hormone exposure
 - Decrease animal products in general
- Use glass whenever possible
- Do not heat or microwave plastic
- Switch to non plastic reusable water bottles
- Avoid pesticides on your lawn and garden



ESTROGEN

- As estrogen exposure increases so does our risk of breast cancer
 - Number of periods in your lifetime
 - BCPs >5 years or current use
 - HRT
 - Endocrine Disrupters
 - **Weight - % body fat**



The Underlying Basis for Obesity: Relationship to Cancer¹

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ABSTRACT An increase in the risk of cancer is one of the consequences of obesity. The predominant cancers associated with obesity have a hormonal base and include breast, prostate, endometrium, colon and gallbladder

An increase in the risk of cancer is one of the consequences of obesity. The increased release of cytokines from this tissue may play a role in the inflammatory state that is associated with obesity (and cancer).

Bray, G, J. Nutr. 2002; 132: 3451S–3455S.

The risk of cancer has been demonstrated to be increased in individuals with a high body mass index (BMI)³. The risk is increased by the system, normal weight is a BMI of 18.5 to <25, overweight is a BMI of 25 to <30 and obesity is a BMI \geq 30. Table 1 shows the prevalence of cancers for overweight individuals with a BMI > 25 and for those who are labeled as obese with a BMI > 30.

The incidence of cancer of the endometrium, breast, colon and gallbladder is increased in women, and the incidence of cancer of the colon and prostate is increased in men. One explanation for these cancers is the increased production of estrogenic compounds by aromatase conversion of androstenedione, produced in the adrenal gland, into estrone. Be-

nature of obesity. The next section provides an overview of the newer ideas that are directing the current research and develop strategies to control obesity and its related

Newer understanding of obesity

Research over the past two decades has provided a unprecedented expansion of our knowledge about the cellular and molecular mechanisms regulating body weight. The greatest impact has resulted from the cloning of genes corresponding to the five mouse monogenic obesity models and the subsequent characterization of the pathways by these genetic entry points. Extensive molecular genetic studies (mouse knockouts) have helped to identify critical players in energy balance as well as validated the importance for previously identified pathways.

As a framework for this discussion, I will use the mouse model. In such a system, afferent signals tell the brain about the state of the external environment related to food. In turn, this central nervous system transduces these messages into efferent control signals that regulate the search for and acquisition of food as well as its subsequent disposal inside the body. Final system ingests, digests, absorbs, transports, store

¹ Presented as part of a symposium, "International Research Conference on Food, Nutrition & Cancer," given by the American Institute for Cancer Research and the World Cancer Research Fund International in Washington, D.C., July 11–12, 2002. This conference was sponsored by BASF Aktiengesellschaft; California Dried Plum Board; The Campbell Soup Company; Danisco Cultor; Galileo Laboratories, Inc.; Mead Johnson Nutritionals; Roche Vitamins, Inc.; and Yamanouchi/Shaklee/NOBYS. Guest editors for this symposium were Helen Norman and Ritva Butrum, American Institute for Cancer Research, Washington, D.C. 20009.

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³ Abbreviations used: BMI, body mass index; C/EBP- β , CCAAT/enhancer binding protein; GLP-1, glucagon-like peptide-1; α -MSH, α -melanocyte-stimulating hormone; PPAR- γ , peroxisome proliferator-activated receptor; PTP-1B, protein tyrosine phosphatase-1B; UCP, uncoupling protein.

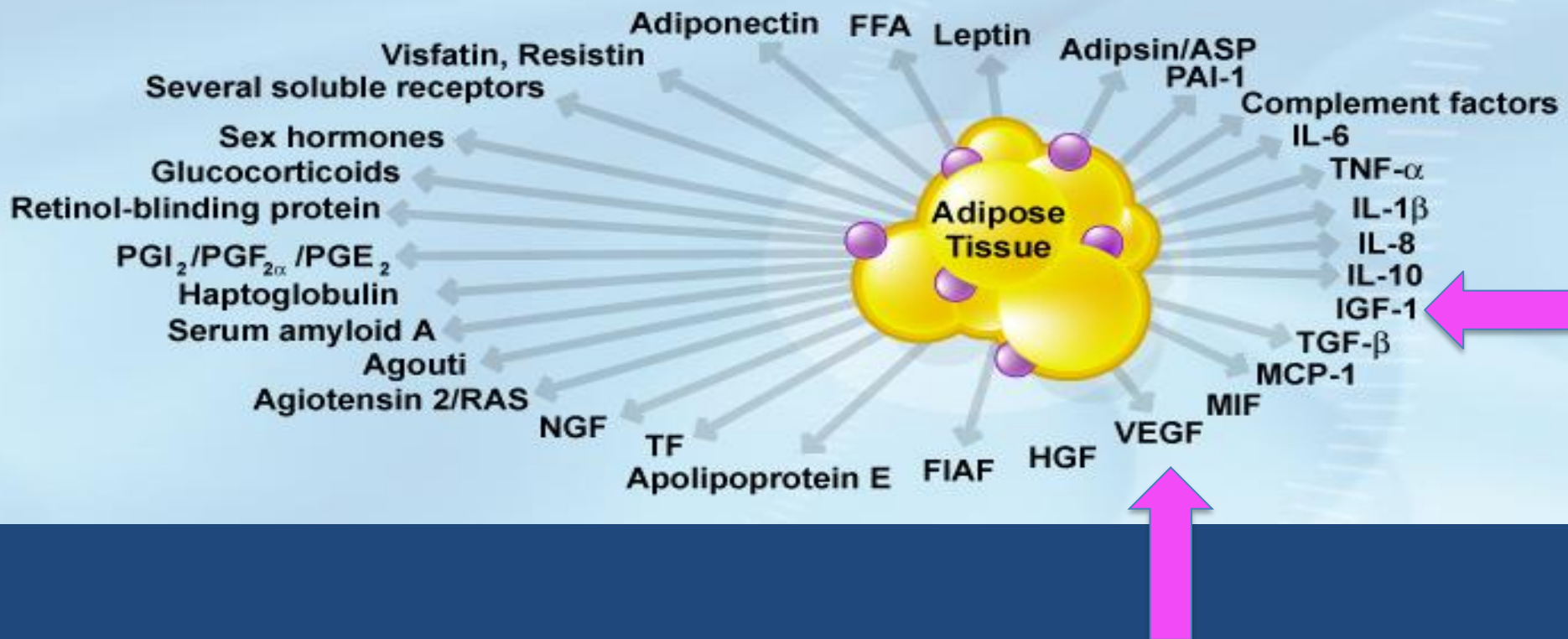


WEIGHT

- Increase weight by **22 or more pounds since age 18... 30% increase** risk of breast cancer than women gained 5 or less pounds
 - JAMA. 2006. 296:193
- Women with the **highest BMI** had a 35 percent **increase in risk** of triple-negative breast cancer and a 39 percent increase in the risk of estrogen receptor-positive breast cancer.
- Women with the **highest levels of physical activity** had **reduced risks** of both triple-negative breast cancer and estrogen receptor-positive breast cancer
 - Phipps A. Cancer Epidemiology, Biomarkers, & Prevention. March 2011
- Breast cancer **survivors** who were **overweight** or obese were more likely to have their cancer **recur** than thinner survivors.
 - Journal of Clinical Oncology. 2002. Vol. 20, No. 15: 3302-3316

Adipose Tissue is an endocrine organ. Very Active.

Bray, G, J. Nutr. 2002; 132: 3451S–3455S.



Obesity

↑ Estrogen synthesis

Insulin resistance

Altered adipokine and cytokine production

Adipocytes

Macrophages

↑ Estradiol

↑ Insulin, ↑ IGF-1

↓ Adiponectin, ↑ leptin

↑ IL-6, IL-1β, ↓ TNFα

↓ Plasma SHBG

↑ Estradiol bioavailability

VEGF induction

Angiogenesis

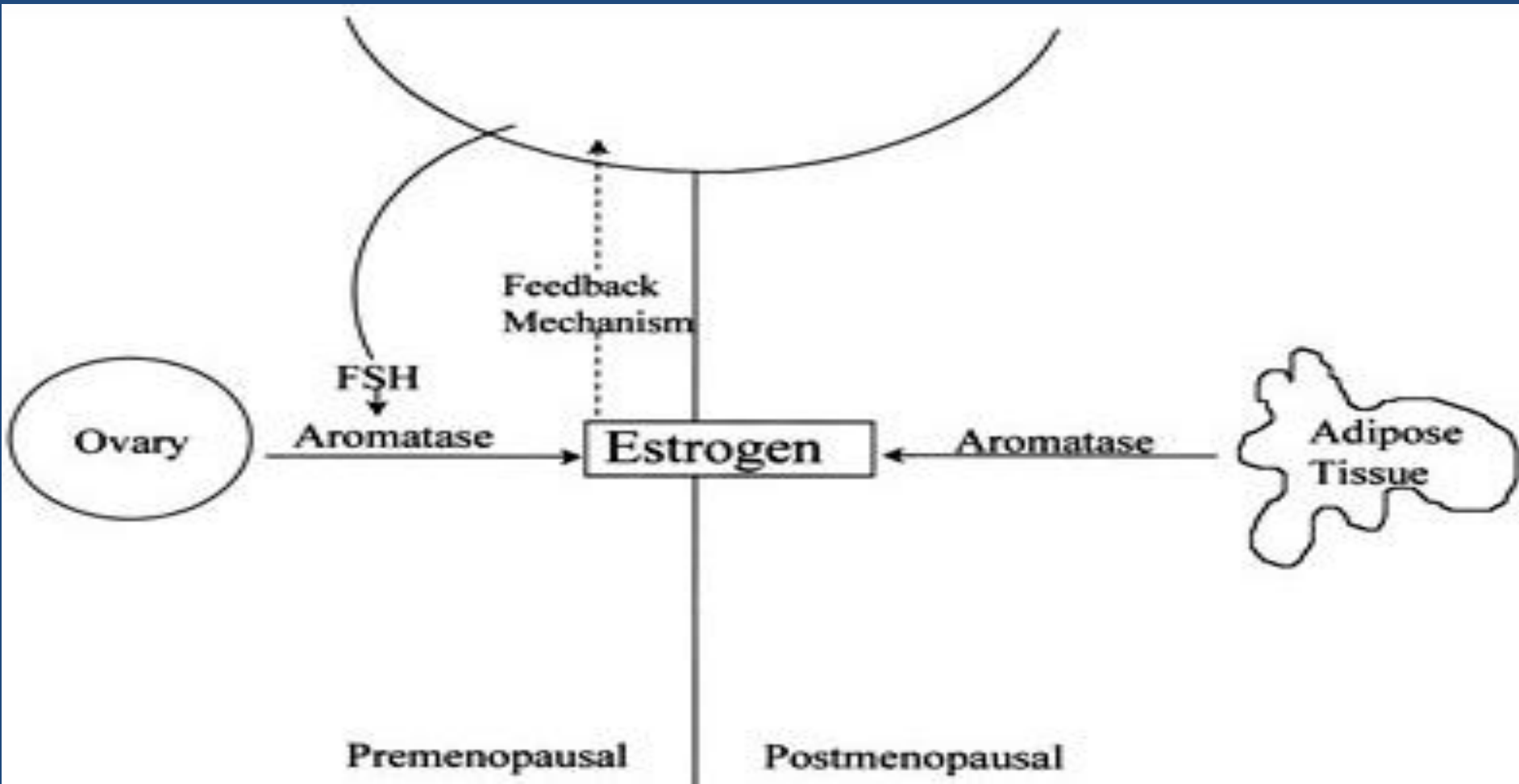
Cell proliferation

Cell survival

Breast cancer cell

WHY?

- Aromatase and Insulin Resistance



Decrease Aromatase

- Lower % body fat
 - Maintain healthy weight
 - Resistance exercise
- Decrease inflammation
 - Omega 3 fats
 - Avoid trans fats
 - Decrease saturated fat
 - Lower % body fat
inflammation made in fat
 - Turmeric
 - Aspirin ?



Decrease Aromatase

- Fiber
- Lignans – Flax seed
- Soy
- Resveratrol
- Grape Seed Extract
- Green Tea
- Brassaiopsis glomerulata



Grape Seed Extract Is an Aromatase Inhibitor and a Suppressor of Aromatase Expression

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Abstract

Aromatase is the enzyme that converts androgen to estrogen. It is expressed at higher levels in breast cancer tissues than normal breast tissues. Grape seed extract (GSE) contains high levels of procyanidin dimers that have been shown in our laboratory to be potent inhibitors of aromatase. In this

cancer cells, is thought to play a more crucial role in stimulating cancer cell growth than circulating estrogen (2).

The human aromatase gene contains nine translated exons (II-X) and at least eight untranslated exon 1's (I.1, I.2, I.3, I.4, I.5, I.6, I.7, and PII). The translation start site is positioned in exon II and one of the 5'-untranslated exon 1's of aromatase mRNA is spliced onto a

Grape Seed Extract Is an Aromatase Inhibitor and a Suppressor of Aromatase Expression

Kijima, I. *Cancer Res* 2006;66:5960-7.

converting C-19 androgen to C-18 estrogen, which is the last and critical step of estrogen synthesis. The female hormone, estrogen, is known to stimulate breast cancer cell growth by binding to the estrogen receptor (ER). Therefore, aromatase and ER are being targeted as a treatment for breast cancer. Aromatase is expressed in a number of tissues such as ovary, placenta, adipose, and bone. The expression of aromatase in breast cancer tissue has been shown by enzyme activity measurement (1-3), immunocytochemistry (4-6), and reverse transcription-PCR (RT-PCR) analysis (7-9). Interestingly, aromatase is found to be expressed at higher levels in breast cancer tissue than normal breast tissues (7-9). The *in situ* produced estrogen, due to overexpressed aromatase in breast

less promoter regulated by glucocorticoid, IFN- γ , and a number of class I cytokine family members such as interleukin (IL)-6 and IL-11 (20, 26, 27).

Our group previously reported that procyanidin B dimers purified from red wine were potent competitive inhibitors of aromatase. Furthermore, procyanidin B dimers were found to reduce androgen-dependent tumor growth in an aromatase-transfected MCF-7 (i.e., MCF-7aro) breast cancer xenograft model (28). This suggests that procyanidin B dimers suppress *in situ* estrogen formation. Procyanidin B dimers are rich in commercially available grape seed extract (GSE). GSE is composed of ~74% to 78% proanthocyanidins and <6% free flavanol monomers such as catechin, epicatechin, and their gallic acid esters. Proanthocyanidins in GSE are known to possess powerful protective properties against free radicals and oxidative stress and have been reported to exhibit a wide range of biological advantages such as antibacterial, antiviral, anti-inflammatory, and antiallergic actions. GSE has also been linked to cancer prevention/therapy because it down-regulated growth factor receptor signaling in prostate



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Isolation and Characterization of Aromatase Inhibitors from *Brassaiopsis glomerulata* (Araliaceae)

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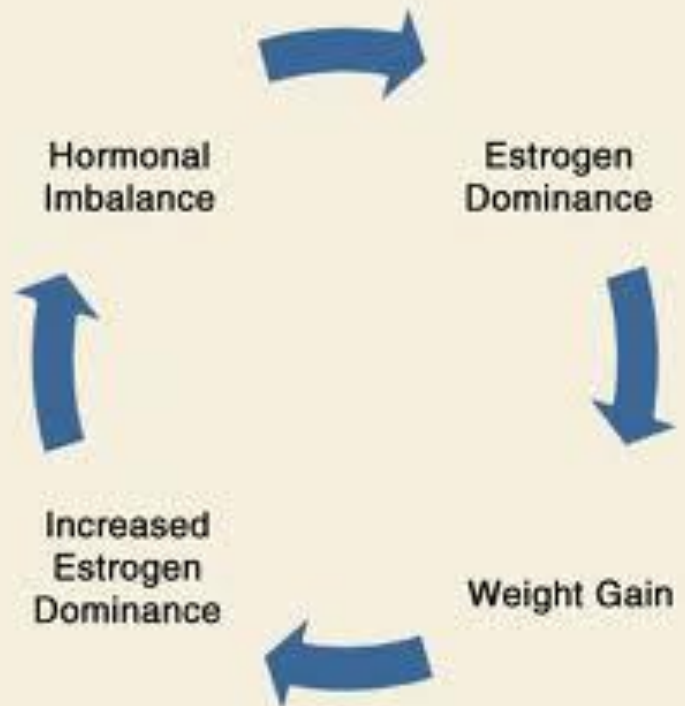
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Abstract

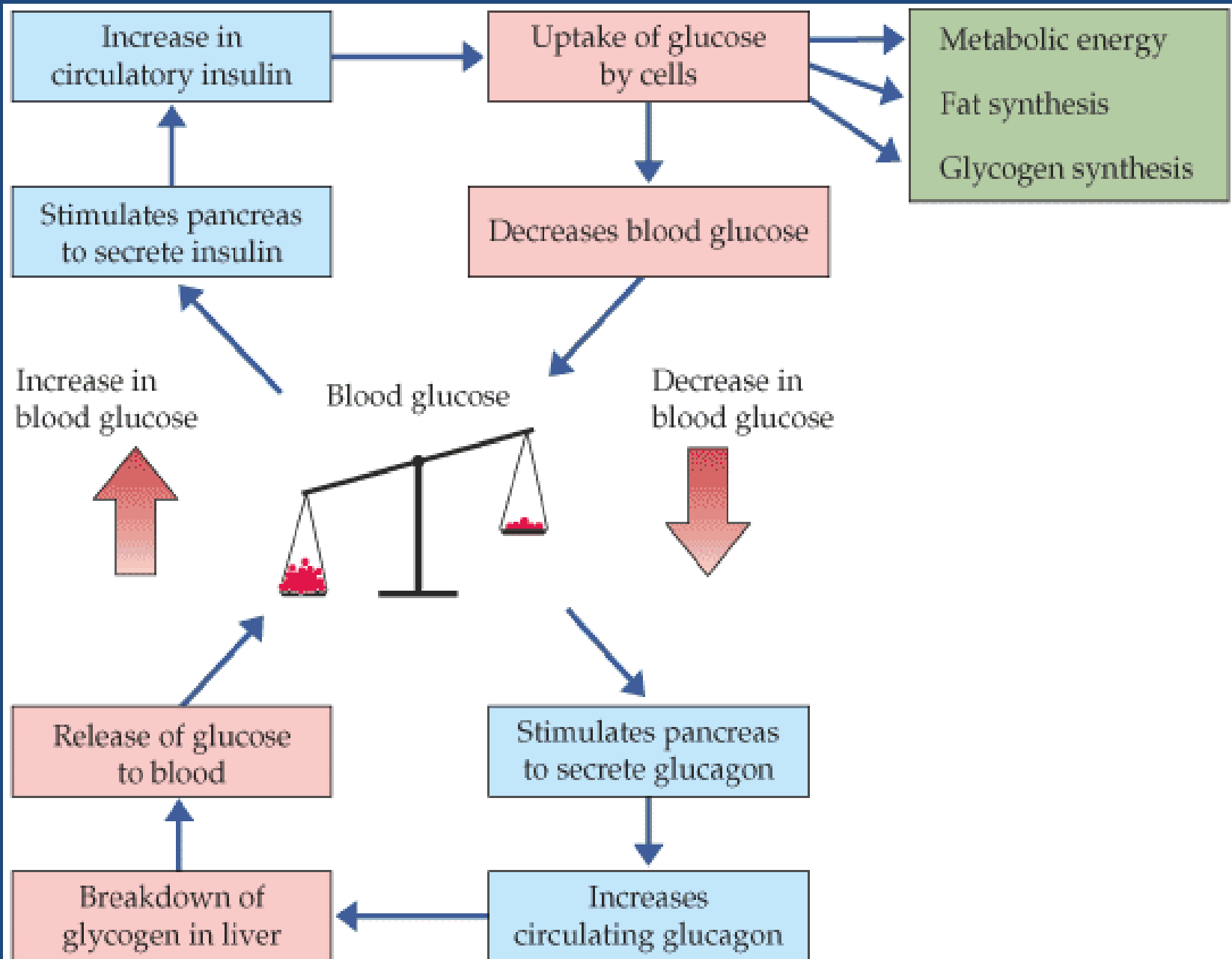
The hexane- and ethyl acetate-soluble extracts of the leaves of *Brassaiopsis glomerulata* (Blume) Regel (Araliaceae), collected in Indonesia, were found to inhibit aromatase, the rate-limiting enzyme in the production of estrogens from androgens, in both enzyme- and cell-based aromatase (AI) assays. Bioassay-guided fractionation led to the isolation of six triterpenoid and triterpenoid classes (1–6) from the hexane extract, of which 6β-hydroxy-11-oxo-12-phenyl-13-oxo-14-phenyl-15-oxo-16-phenyl-17-oxo-18-phenyl-19-oxo-20-phenyl-21-oxo-22-phenyl-23-oxo-24-phenyl-25-oxo-26-phenyl-27-oxo-28-phenyl-29-oxo-30-phenyl-31-oxo-32-phenyl-33-oxo-34-phenyl-35-oxo-36-phenyl-37-oxo-38-phenyl-39-oxo-40-phenyl-41-oxo-42-phenyl-43-oxo-44-phenyl-45-oxo-46-phenyl-47-oxo-48-phenyl-49-oxo-50-phenyl-51-oxo-52-phenyl-53-oxo-54-phenyl-55-oxo-56-phenyl-57-oxo-58-phenyl-59-oxo-60-phenyl-61-oxo-62-phenyl-63-oxo-64-phenyl-65-oxo-66-phenyl-67-oxo-68-phenyl-69-oxo-70-phenyl-71-oxo-72-phenyl-73-oxo-74-phenyl-75-oxo-76-phenyl-77-oxo-78-phenyl-79-oxo-80-phenyl-81-oxo-82-phenyl-83-oxo-84-phenyl-85-oxo-86-phenyl-87-oxo-88-phenyl-89-oxo-90-phenyl-91-oxo-92-phenyl-93-oxo-94-phenyl-95-oxo-96-phenyl-97-oxo-98-phenyl-99-oxo-100-phenyl-101-oxo-102-phenyl-103-oxo-104-phenyl-105-oxo-106-phenyl-107-oxo-108-phenyl-109-oxo-110-phenyl-111-oxo-112-phenyl-113-oxo-114-phenyl-115-oxo-116-phenyl-117-oxo-118-phenyl-119-oxo-120-phenyl-121-oxo-122-phenyl-123-oxo-124-phenyl-125-oxo-126-phenyl-127-oxo-128-phenyl-129-oxo-130-phenyl-131-oxo-132-phenyl-133-oxo-134-phenyl-135-oxo-136-phenyl-137-oxo-138-phenyl-139-oxo-140-phenyl-141-oxo-142-phenyl-143-oxo-144-phenyl-145-oxo-146-phenyl-147-oxo-148-phenyl-149-oxo-150-phenyl-151-oxo-152-phenyl-153-oxo-154-phenyl-155-oxo-156-phenyl-157-oxo-158-phenyl-159-oxo-160-phenyl-161-oxo-162-phenyl-163-oxo-164-phenyl-165-oxo-166-phenyl-167-oxo-168-phenyl-169-oxo-170-phenyl-171-oxo-172-phenyl-173-oxo-174-phenyl-175-oxo-176-phenyl-177-oxo-178-phenyl-179-oxo-180-phenyl-181-oxo-182-phenyl-183-oxo-184-phenyl-185-oxo-186-phenyl-187-oxo-188-phenyl-189-oxo-190-phenyl-191-oxo-192-phenyl-193-oxo-194-phenyl-195-oxo-196-phenyl-197-oxo-198-phenyl-199-oxo-200-phenyl-201-oxo-202-phenyl-203-oxo-204-phenyl-205-oxo-206-phenyl-207-oxo-208-phenyl-209-oxo-210-phenyl-211-oxo-212-phenyl-213-oxo-214-phenyl-215-oxo-216-phenyl-217-oxo-218-phenyl-219-oxo-220-phenyl-221-oxo-222-phenyl-223-oxo-224-phenyl-225-oxo-226-phenyl-227-oxo-228-phenyl-229-oxo-230-phenyl-231-oxo-232-phenyl-233-oxo-234-phenyl-235-oxo-236-phenyl-237-oxo-238-phenyl-239-oxo-240-phenyl-241-oxo-242-phenyl-243-oxo-244-phenyl-245-oxo-246-phenyl-247-oxo-248-phenyl-249-oxo-250-phenyl-251-oxo-252-phenyl-253-oxo-254-phenyl-255-oxo-256-phenyl-257-oxo-258-phenyl-259-oxo-260-phenyl-261-oxo-262-phenyl-263-oxo-264-phenyl-265-oxo-266-phenyl-267-oxo-268-phenyl-269-oxo-270-phenyl-271-oxo-272-phenyl-273-oxo-274-phenyl-275-oxo-276-phenyl-277-oxo-278-phenyl-279-oxo-280-phenyl-281-oxo-282-phenyl-283-oxo-284-phenyl-285-oxo-286-phenyl-287-oxo-288-phenyl-289-oxo-290-phenyl-291-oxo-292-phenyl-293-oxo-294-phenyl-295-oxo-296-phenyl-297-oxo-298-phenyl-299-oxo-300-phenyl-301-oxo-302-phenyl-303-oxo-304-phenyl-305-oxo-306-phenyl-307-oxo-308-phenyl-309-oxo-310-phenyl-311-oxo-312-phenyl-313-oxo-314-phenyl-315-oxo-316-phenyl-317-oxo-318-phenyl-319-oxo-320-phenyl-321-oxo-322-phenyl-323-oxo-324-phenyl-325-oxo-326-phenyl-327-oxo-328-phenyl-329-oxo-330-phenyl-331-oxo-332-phenyl-333-oxo-334-phenyl-335-oxo-336-phenyl-337-oxo-338-phenyl-339-oxo-340-phenyl-341-oxo-342-phenyl-343-oxo-344-phenyl-345-oxo-346-phenyl-347-oxo-348-phenyl-349-oxo-350-phenyl-351-oxo-352-phenyl-353-oxo-354-phenyl-355-oxo-356-phenyl-357-oxo-358-phenyl-359-oxo-360-phenyl-361-oxo-362-phenyl-363-oxo-364-phenyl-365-oxo-366-phenyl-367-oxo-368-phenyl-369-oxo-370-phenyl-371-oxo-372-phenyl-373-oxo-374-phenyl-375-oxo-376-phenyl-377-oxo-378-phenyl-379-oxo-380-phenyl-381-oxo-382-phenyl-383-oxo-384-phenyl-385-oxo-386-phenyl-387-oxo-388-phenyl-389-oxo-390-phenyl-391-oxo-392-phenyl-393-oxo-394-phenyl-395-oxo-396-phenyl-397-oxo-398-phenyl-399-oxo-400-phenyl-401-oxo-402-phenyl-403-oxo-404-phenyl-405-oxo-406-phenyl-407-oxo-408-phenyl-409-oxo-410-phenyl-411-oxo-412-phenyl-413-oxo-414-phenyl-415-oxo-416-phenyl-417-oxo-418-phenyl-419-oxo-420-phenyl-421-oxo-422-phenyl-423-oxo-424-phenyl-425-oxo-426-phenyl-427-oxo-428-phenyl-429-oxo-430-phenyl-431-oxo-432-phenyl-433-oxo-434-phenyl-435-oxo-436-phenyl-437-oxo-438-phenyl-439-oxo-440-phenyl-441-oxo-442-phenyl-443-oxo-444-phenyl-445-oxo-446-phenyl-447-oxo-448-phenyl-449-oxo-450-phenyl-451-oxo-452-phenyl-453-oxo-454-phenyl-455-oxo-456-phenyl-457-oxo-458-phenyl-459-oxo-460-phenyl-461-oxo-462-phenyl-463-oxo-464-phenyl-465-oxo-466-phenyl-467-oxo-468-phenyl-469-oxo-470-phenyl-471-oxo-472-phenyl-473-oxo-474-phenyl-475-oxo-476-phenyl-477-oxo-478-phenyl-479-oxo-480-phenyl-481-oxo-482-phenyl-483-oxo-484-phenyl-485-oxo-486-phenyl-487-oxo-488-phenyl-489-oxo-490-phenyl-491-oxo-492-phenyl-493-oxo-494-phenyl-495-oxo-496-phenyl-497-oxo-498-phenyl-499-oxo-500-phenyl-501-oxo-502-phenyl-503-oxo-504-phenyl-505-oxo-506-phenyl-507-oxo-508-phenyl-509-oxo-510-phenyl-511-oxo-512-phenyl-513-oxo-514-phenyl-515-oxo-516-phenyl-517-oxo-518-phenyl-519-oxo-520-phenyl-521-oxo-522-phenyl-523-oxo-524-phenyl-525-oxo-526-phenyl-527-oxo-528-phenyl-529-oxo-530-phenyl-531-oxo-532-phenyl-533-oxo-534-phenyl-535-oxo-536-phenyl-537-oxo-538-phenyl-539-oxo-540-phenyl-541-oxo-542-phenyl-543-oxo-544-phenyl-545-oxo-546-phenyl-547-oxo-548-phenyl-549-oxo-550-phenyl-551-oxo-552-phenyl-553-oxo-554-phenyl-555-oxo-556-phenyl-557-oxo-558-phenyl-559-oxo-560-phenyl-561-oxo-562-phenyl-563-oxo-564-phenyl-565-oxo-566-phenyl-567-oxo-568-phenyl-569-oxo-570-phenyl-571-oxo-572-phenyl-573-oxo-574-phenyl-575-oxo-576-phenyl-577-oxo-578-phenyl-579-oxo-580-phenyl-581-oxo-582-phenyl-583-oxo-584-phenyl-585-oxo-586-phenyl-587-oxo-588-phenyl-589-oxo-590-phenyl-591-oxo-592-phenyl-593-oxo-594-phenyl-595-oxo-596-phenyl-597-oxo-598-phenyl-599-oxo-600-phenyl-601-oxo-602-phenyl-603-oxo-604-phenyl-605-oxo-606-phenyl-607-oxo-608-phenyl-609-oxo-610-phenyl-611-oxo-612-phenyl-613-oxo-614-phenyl-615-oxo-616-phenyl-617-oxo-618-phenyl-619-oxo-620-phenyl-621-oxo-622-phenyl-623-oxo-624-phenyl-625-oxo-626-phenyl-627-oxo-628-phenyl-629-oxo-630-phenyl-631-oxo-632-phenyl-633-oxo-634-phenyl-635-oxo-636-phenyl-637-oxo-638-phenyl-639-oxo-640-phenyl-641-oxo-642-phenyl-643-oxo-644-phenyl-645-oxo-646-phenyl-647-oxo-648-phenyl-649-oxo-650-phenyl-651-oxo-652-phenyl-653-oxo-654-phenyl-655-oxo-656-phenyl-657-oxo-658-phenyl-659-oxo-660-phenyl-661-oxo-662-phenyl-663-oxo-664-phenyl-665-oxo-666-phenyl-667-oxo-668-phenyl-669-oxo-670-phenyl-671-oxo-672-phenyl-673-oxo-674-phenyl-675-oxo-676-phenyl-677-oxo-678-phenyl-679-oxo-680-phenyl-681-oxo-682-phenyl-683-oxo-684-phenyl-685-oxo-686-phenyl-687-oxo-688-phenyl-689-oxo-690-phenyl-691-oxo-692-phenyl-693-oxo-694-phenyl-695-oxo-696-phenyl-697-oxo-698-phenyl-699-oxo-700-phenyl-701-oxo-702-phenyl-703-oxo-704-phenyl-705-oxo-706-phenyl-707-oxo-708-phenyl-709-oxo-710-phenyl-711-oxo-712-phenyl-713-oxo-714-phenyl-715-oxo-716-phenyl-717-oxo-718-phenyl-719-oxo-720-phenyl-721-oxo-722-phenyl-723-oxo-724-phenyl-725-oxo-726-phenyl-727-oxo-728-phenyl-729-oxo-730-phenyl-731-oxo-732-phenyl-733-oxo-734-phenyl-735-oxo-736-phenyl-737-oxo-738-phenyl-739-oxo-740-phenyl-741-oxo-742-phenyl-743-oxo-744-phenyl-745-oxo-746-phenyl-747-oxo-748-phenyl-749-oxo-750-phenyl-751-oxo-752-phenyl-753-oxo-754-phenyl-755-oxo-756-phenyl-757-oxo-758-phenyl-759-oxo-760-phenyl-761-oxo-762-phenyl-763-oxo-764-phenyl-765-oxo-766-phenyl-767-oxo-768-phenyl-769-oxo-770-phenyl-771-oxo-772-phenyl-773-oxo-774-phenyl-775-oxo-776-phenyl-777-oxo-778-phenyl-779-oxo-780-phenyl-781-oxo-782-phenyl-783-oxo-784-phenyl-785-oxo-786-phenyl-787-oxo-788-phenyl-789-oxo-790-phenyl-791-oxo-792-phenyl-793-oxo-794-phenyl-795-oxo-796-phenyl-797-oxo-798-phenyl-799-oxo-800-phenyl-801-oxo-802-phenyl-803-oxo-804-phenyl-805-oxo-806-phenyl-807-oxo-808-phenyl-809-oxo-810-phenyl-811-oxo-812-phenyl-813-oxo-814-phenyl-815-oxo-816-phenyl-817-oxo-818-phenyl-819-oxo-820-phenyl-821-oxo-822-phenyl-823-oxo-824-phenyl-825-oxo-826-phenyl-827-oxo-828-phenyl-829-oxo-830-phenyl-831-oxo-832-phenyl-833-oxo-834-phenyl-835-oxo-836-phenyl-837-oxo-838-phenyl-839-oxo-840-phenyl-841-oxo-842-phenyl-843-oxo-844-phenyl-845-oxo-846-phenyl-847-oxo-848-phenyl-849-oxo-850-phenyl-851-oxo-852-phenyl-853-oxo-854-phenyl-855-oxo-856-phenyl-857-oxo-858-phenyl-859-oxo-860-phenyl-861-oxo-862-phenyl-863-oxo-864-phenyl-865-oxo-866-phenyl-867-oxo-868-phenyl-869-oxo-870-phenyl-871-oxo-872-phenyl-873-oxo-874-phenyl-875-oxo-876-phenyl-877-oxo-878-phenyl-879-oxo-880-phenyl-881-oxo-882-phenyl-883-oxo-884-phenyl-885-oxo-886-phenyl-887-oxo-888-phenyl-889-oxo-890-phenyl-891-oxo-892-phenyl-893-oxo-894-phenyl-895-oxo-896-phenyl-897-oxo-898-phenyl-899-oxo-900-phenyl-901-oxo-902-phenyl-903-oxo-904-phenyl-905-oxo-906-phenyl-907-oxo-908-phenyl-909-oxo-910-phenyl-911-oxo-912-phenyl-913-oxo-914-phenyl-915-oxo-916-phenyl-917-oxo-918-phenyl-919-oxo-920-phenyl-921-oxo-922-phenyl-923-oxo-924-phenyl-925-oxo-926-phenyl-927-oxo-928-phenyl-929-oxo-930-phenyl-931-oxo-932-phenyl-933-oxo-934-phenyl-935-oxo-936-phenyl-937-oxo-938-phenyl-939-oxo-940-phenyl-941-oxo-942-phenyl-943-oxo-944-phenyl-945-oxo-946-phenyl-947-oxo-948-phenyl-949-oxo-950-phenyl-951-oxo-952-phenyl-953-oxo-954-phenyl-955-oxo-956-phenyl-957-oxo-958-phenyl-959-oxo-960-phenyl-961-oxo-962-phenyl-963-oxo-964-phenyl-965-oxo-966-phenyl-967-oxo-968-phenyl-969-oxo-970-phenyl-971-oxo-972-phenyl-973-oxo-974-phenyl-975-oxo-976-phenyl-977-oxo-978-phenyl-979-oxo-980-phenyl-981-oxo-982-phenyl-983-oxo-984-phenyl-985-oxo-986-phenyl-987-oxo-988-phenyl-989-oxo-990-phenyl-991-oxo-992-phenyl-993-oxo-994-phenyl-995-oxo-996-phenyl-997-oxo-998-phenyl-999-oxo-1000-phenyl-1001-oxo-1002-phenyl-1003-oxo-1004-phenyl-1005-oxo-1006-phenyl-1007-oxo-1008-phenyl-1009-oxo-1010-phenyl-1011-oxo-1012-phenyl-1013-oxo-1014-phenyl-1015-oxo-1016-phenyl-1017-oxo-1018-phenyl-1019-oxo-1020-phenyl-1021-oxo-1022-phenyl-1023-oxo-1024-phenyl-1025-oxo-1026-phenyl-1027-oxo-1028-phenyl-1029-oxo-1030-phenyl-1031-oxo-1032-phenyl-1033-oxo-1034-phenyl-1035-oxo-1036-phenyl-1037-oxo-1038-phenyl-1039-oxo-1040-phenyl-1041-oxo-1042-phenyl-1043-oxo-1044-phenyl-1045-oxo-1046-phenyl-1047-oxo-1048-phenyl-1049-oxo-1050-phenyl-1051-oxo-1052-phenyl-1053-oxo-1054-phenyl-1055-oxo-1056-phenyl-1057-oxo-1058-phenyl-1059-oxo-1060-phenyl-1061-oxo-1062-phenyl-1063-oxo-1064-phenyl-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SHBG

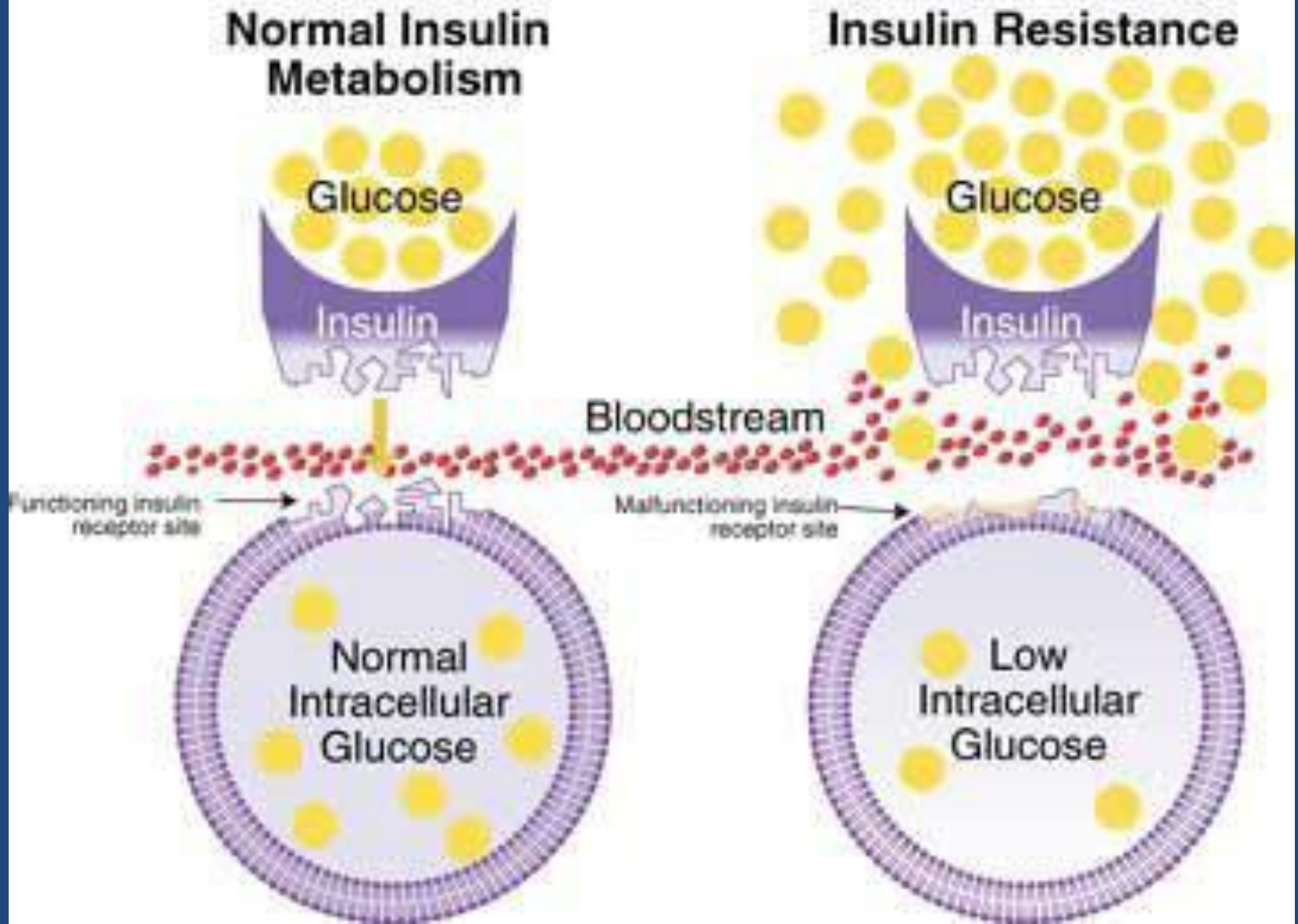
- Sex Hormone Binding Globulin
- Increased level = lower free estrogen
 - Maintain a healthy weight
 - Vegetarian lower fat diet
 - Improve Insulin Sensitivity



Blood Sugar Regulation



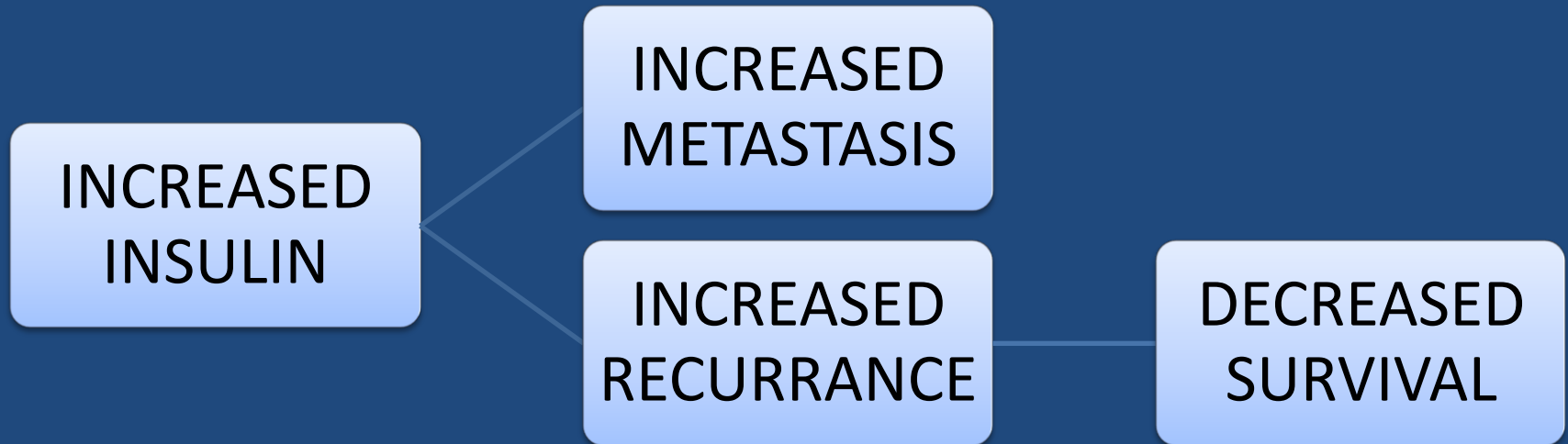
Insulin Resistance



Insulin Resistance

- Women with higher levels of insulin were 2.5 x more likely to have breast cancer over the next 7 years than women with the lowest insulin levels
 - 800 women without diabetes
 - not taking estrogen
 - J. Natl. Cancer Inst. 101:48, 2009.

Insulin Resistance



Diabetes Care 33:1304, 2010.



Review

The pancreatic β -cell as a target of estrogens and xenoestrogens: Implications for blood glucose homeostasis and diabetes

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ABSTRACT

The estrogen receptor ER α is emerging as a key molecule involved in glucose and lipid metabolism. The main functions of pancreatic β -cells are the biosynthesis and release of insulin, the only hormone that can directly decrease blood glucose levels. Estrogen receptors ER α and ER β exist in β -cells. The role of ER β is still unknown, yet ER α plays an important role in the regulation of insulin biosynthesis, insulin secretion and β -cell survival. Activation of ER α by 17 β -estradiol (E2) and the environmental estrogen bisphenol-A (BPA) promotes an increase of insulin biosynthesis through a non-classical estrogen-activated pathway that involves phosphorylation of ERK1/2. The activation of ER α by physiological concentrations of E2 may play an important role in the adaptation of the endocrine pancreas to pregnancy. However, if ER α is over stimulated by an excess of E2 or the action of an environmental estrogen such as BPA, it will produce an excessive insulin signaling. This may provoke insulin resistance in the liver and muscle, as well as β -cell

Contents

1. The role of the endocrine disruptors
 2. Estrogens, estrogen receptors and β -cell failure
 3. The role of the estradiol and BPA
 4. E2 and BPA are equivalent in the activation of ER α
 5. Physiological and pathological roles of ER α
 6. Concluding remarks
- Acknowledgments
References

1. The role of the endocrine disruptors on blood glucose homeostasis

Blood glucose levels fluctuate throughout the day, in order to maintain a constant level. This process, defined as glucose homeostasis, is a complex communication between the endocrine system, skeletal muscle, adipose tissue and the liver (Herman and Kahn, 2000).

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Therefore, although two of the main causes of β -cell failure in type 2 diabetes are overnutrition and lack of exercise, environmental estrogens, in particular BPA, are strong candidates to exacerbate and accelerate the development of type 2 Diabetes.

Insulin Resistance

- Abdominal weight gain
- Fatigue
- Feeling tired after a meal
- Harder time losing weight
- Cravings for foods
- Hot Flashes
- Energy Swings
- Low blood sugar



Who Is At Risk?

- **Epidemic**

- 5% of children
- 34% of adults over age 20
- 51% of people over age 60

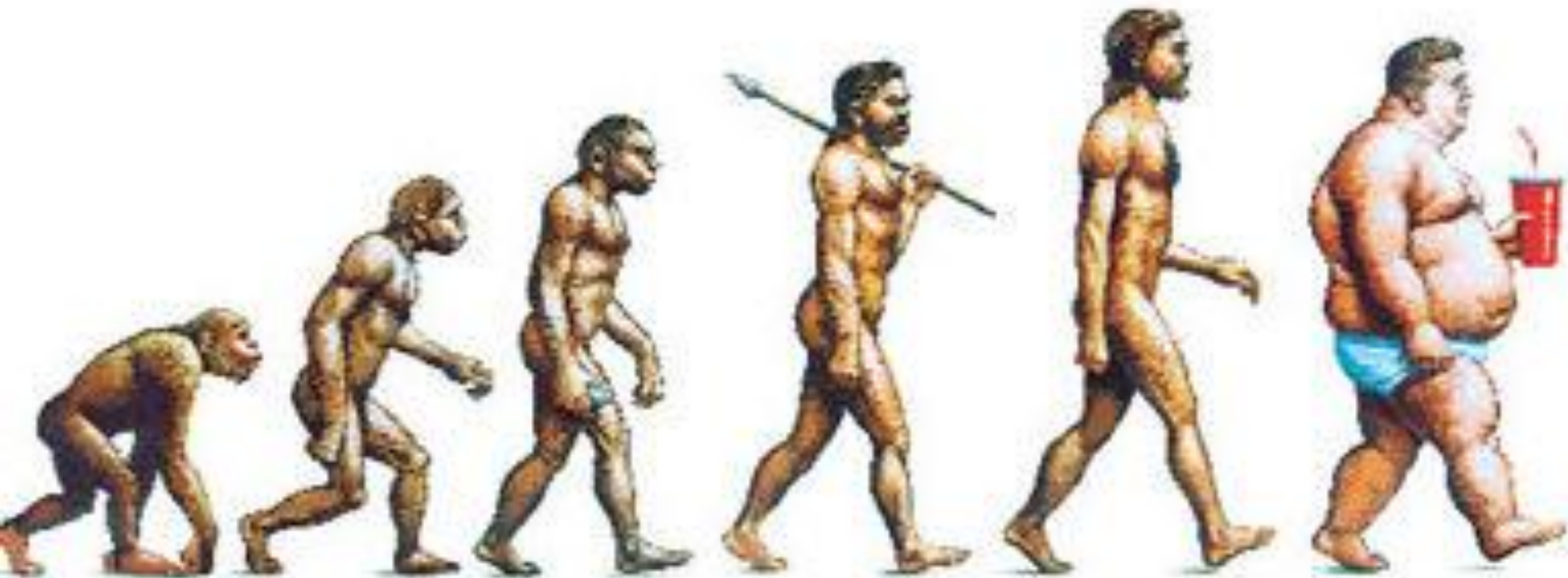
National Health Statistics Report, CDC.
No 13, May 2009

- **Lifestyle**

- Weight gain
- Poor Diet
- Lack of exercise
- Stress
- Sleep deprivation
- Dysbiosis
- Toxin



Our Genes Haven't Changed, But Our Environment Has...

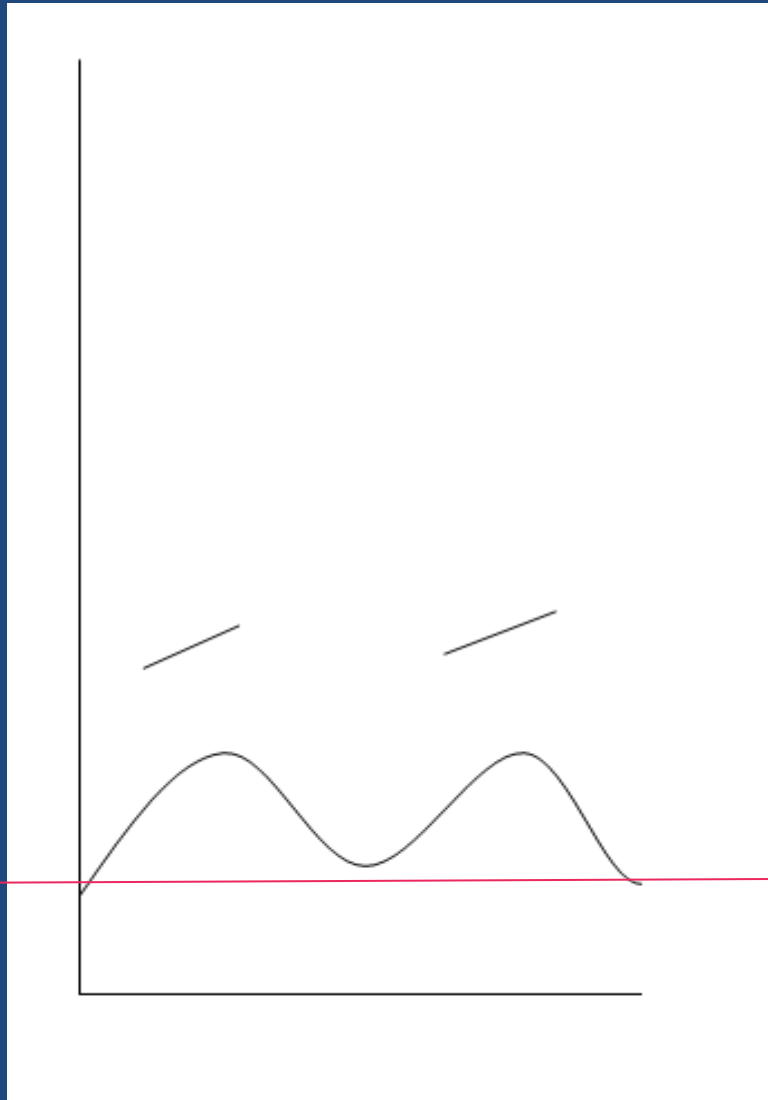


Normal blood sugar and insulin levels

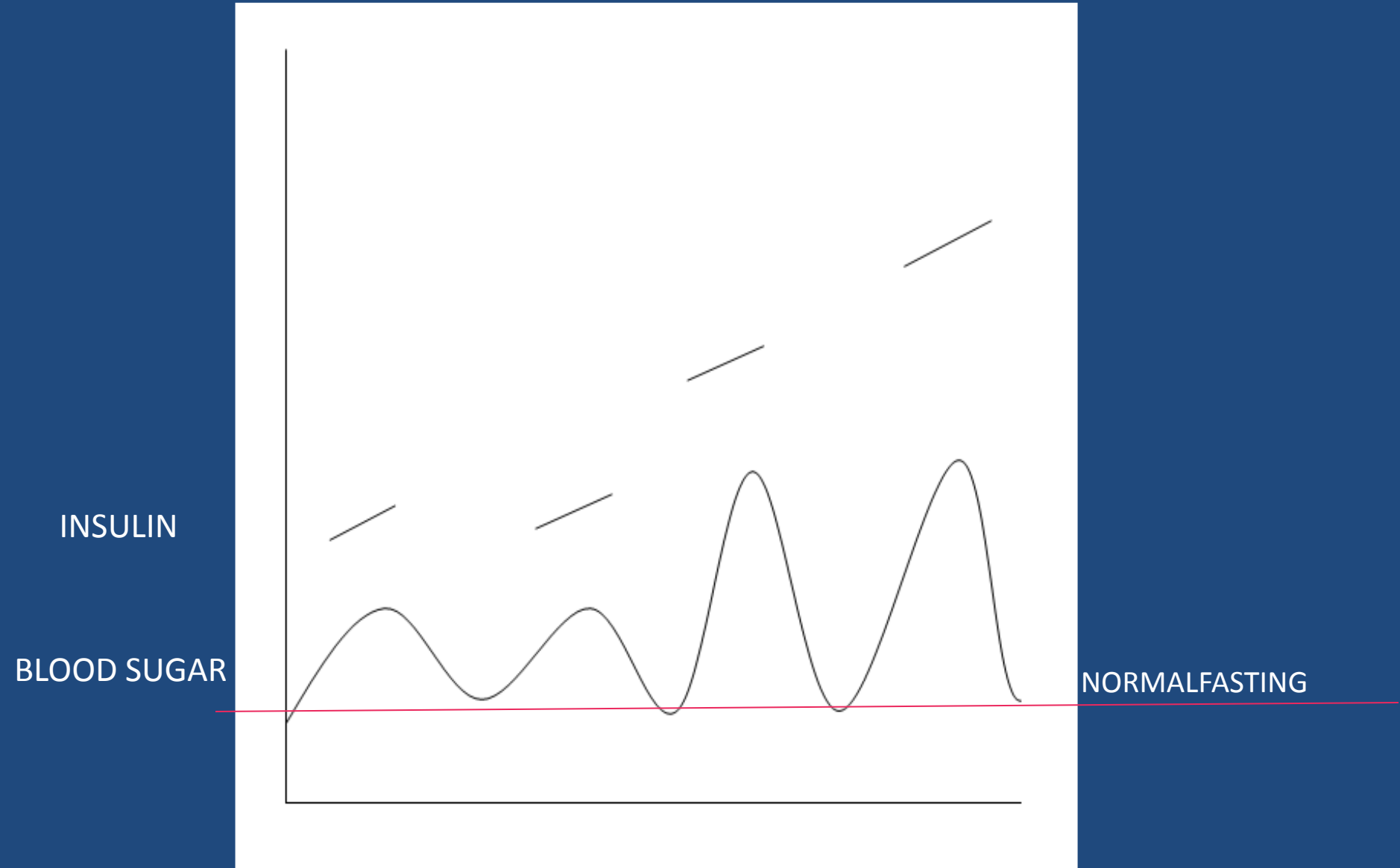
INSULIN

BLOOD SUGAR

NORMAL FASTING



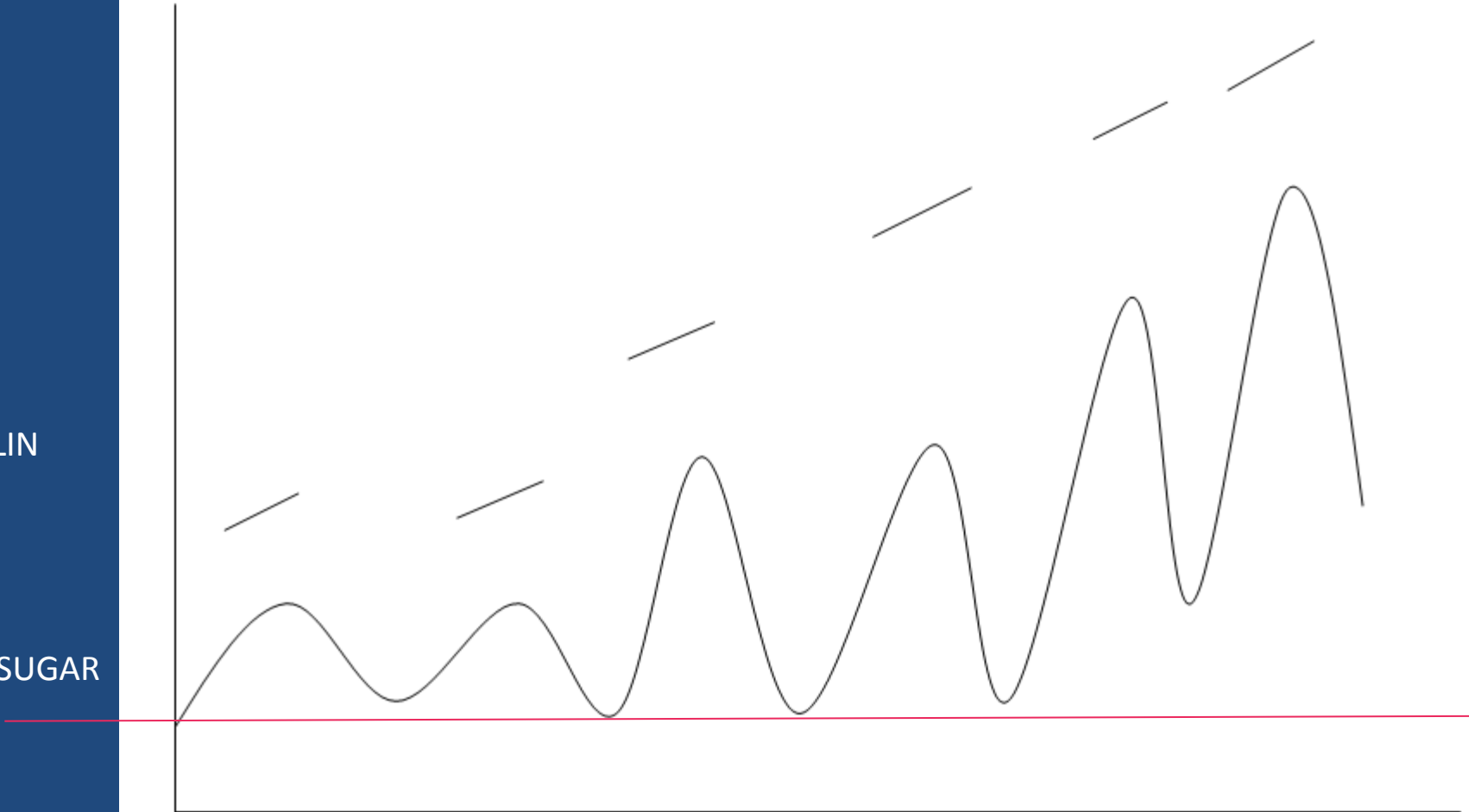
Insulin Resistance



Normal → Insulin Resistance → Diabetes

INSULIN

BLOOD SUGAR



METABOLIC SYNDROME

3 out of the 5

1. Impaired glucose tolerance –
 - fasting blood sugar > 100 or high insulin
2. Elevated blood pressure
 - $>130/85$ or on medication
3. Central Obesity = Apple shape
 - Waist circumference >35 " women
 - Waist / Hip ratio $> .80$ women
4. Elevated Triglycerides > 150
5. Low HDL < 50 women

How Can I Improve Insulin Sensitivity?

- Increase **fiber** - 35 grams daily
- Protein - at each meal
- Regular Meals
- Increase omega 3 fats
- Eliminate Trans fats (partially hydrogenated fats)
- Nutrient dense foods
- 40 minutes of **exercise** daily
- Get 7-9 hours of **sleep** per night
- Manage stress

Glycemic Load Linked To Breast Cancer Risk

- *61,000 women over 17 years*
- *Highest Glycemic Load had about 80% increased risk of getting ER+ breast cancer*

Int J Cancer 2009;125:153-157.



ESTROGEN METABOLISM

- 2 OH Estrone - protective
- 4 OH Estrone - promote tissue proliferation and carcinogenic
- 16 OH Estrone - promotes tissue proliferation and carcinogenic

- 2/16 ratio > 2 optimal

Improve Estrogen Metabolism

- Increase cruciferous vegetables
I3C and DIM and Sulforaphane
- Fish oil
- Daily exercise
- Ground flax seed
- Healthy soy



Some Genes

- BRCA 1 and 2
- COMT
- CYP1B1
- GSTM1
- MTHFR

DETOXIFICATION

- Phase I - certain people have higher risk
 - Avoid Estrogen Disrupters
 - Avoid Cigarette smoke
 - Decrease Charbroiled Meats -
Heterocyclic aromatic amines
 - Limit Alcohol

ALCOHOL

- As alcohol intake increases so does our risk
- Linear Relationship

Chen, W. JAMA,2011;306:1884-1890.

- For every 1 drink increase per day, a women's risk of getting breast cancer increased by 12%

J Nat Cancer Inst.2009;101:296-305

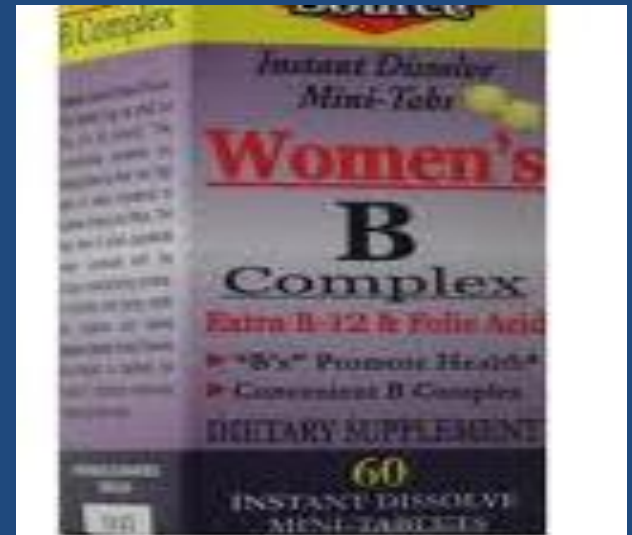
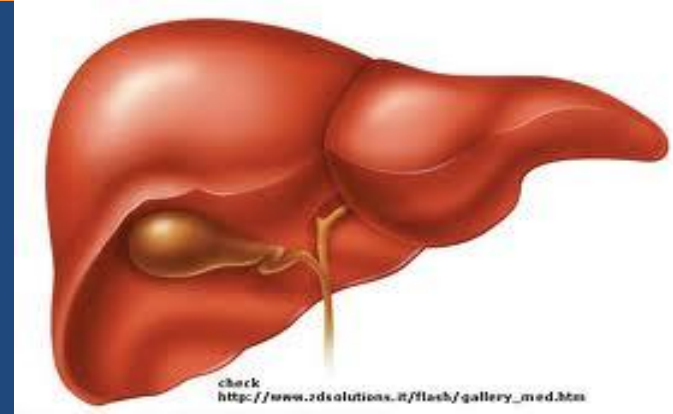
- >2 drinks per day
= 3x increased risk

Annals of Int Medicine 11/02.



ALCOHOL - Why?

- Liver and detox impact
- Increase free estrogen
 - by decreasing SHBG
- Associated with other unhealthy lifestyles
- Decrease B vitamins
 - important for methylation
 - Chen, W. JAMA,2011;306:1884–1890.



DETOXIFICATION

- Phase II
 - Methylation
 - Need adequate folate, B12, B6
 - Alcohol increases B vitamin needs
 - Genes - MTHFR
 - Check homocysteine
 - Methylmalonic acid
 - Sulfation
 - Cysteine ---- glutathione
 - Glucuronidation
 - Calcium d glucurate
 - 1000mg 2x day



Glucuronidation

- Glucuronic Acid conjugates with estrogen
- E-GA - excreted in the stool
- Beta glucuronidase - cleave E-GA and increases free estrogen
- Beta glucuronidase is elevated:
 - high meat / low fiber diets
 - Imbalanced gut flora
 - Pathogenic gut flora



Unhealthy
Bacteria

Increased beta
glucuronidase

Cleaves
estrogen from
glucuronic
acid

Increased free
estrogen and
estrogen
reabsorption

Healthy gut
bacteria

Soluble Fiber

Increased
butyrate

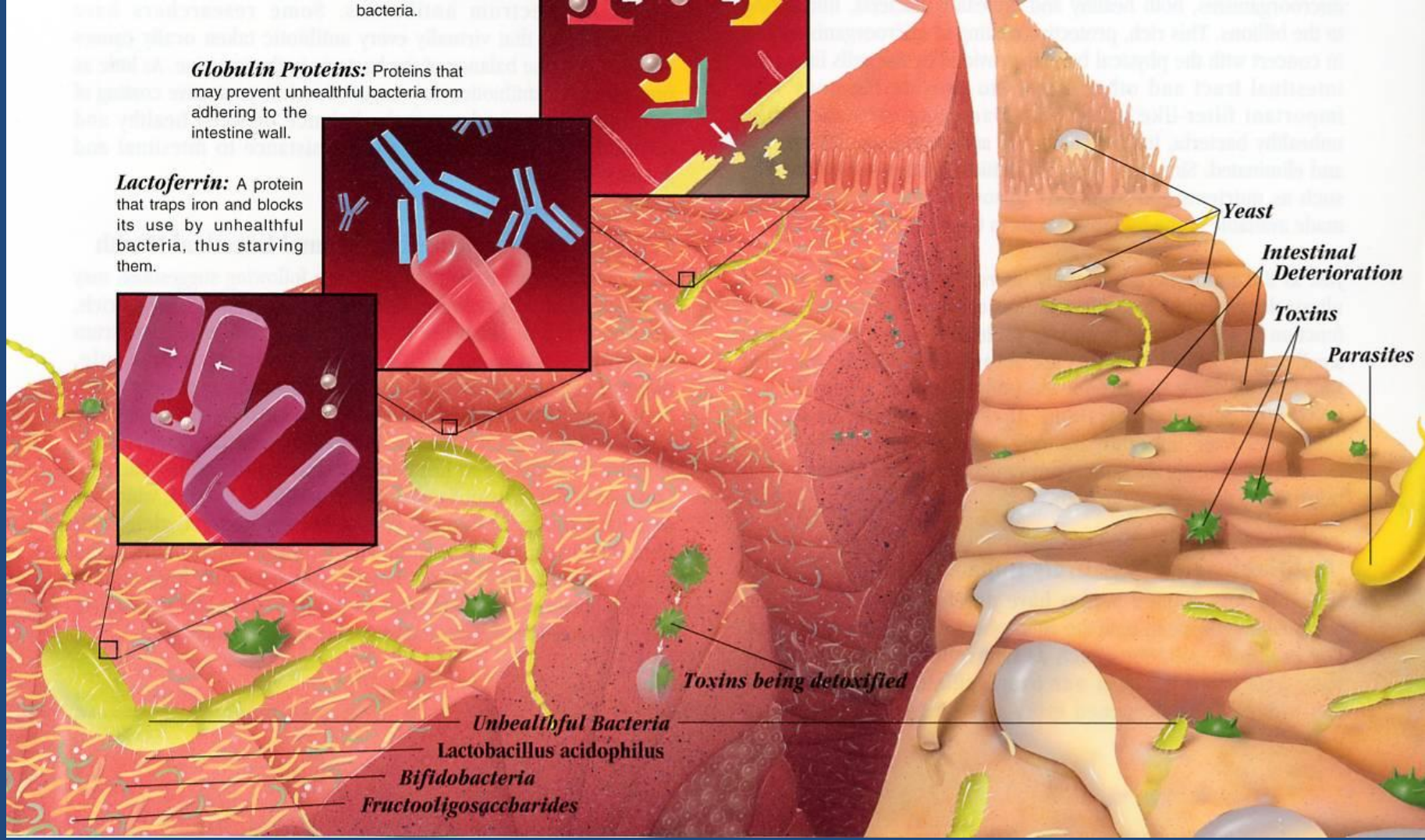
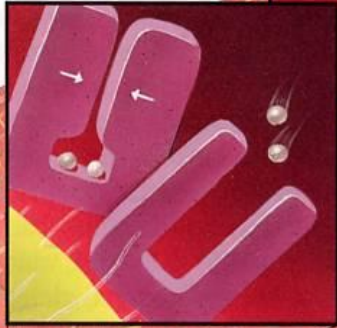
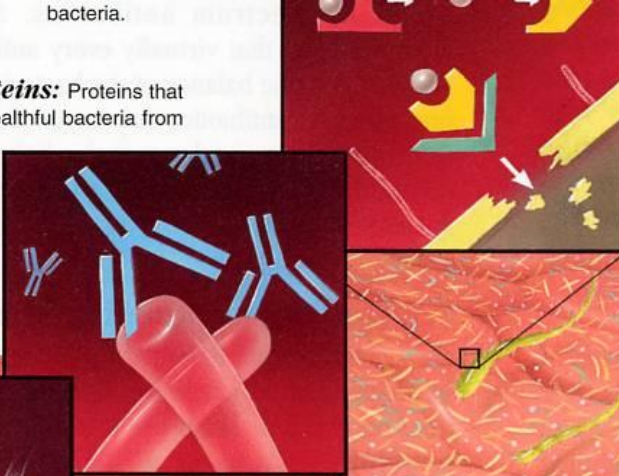
Decreased
inflammation
and cancer

Gut Microbiome

bacteria.

Globulin Proteins: Proteins that may prevent unhealthful bacteria from adhering to the intestine wall.

Lactoferrin: A protein that traps iron and blocks its use by unhealthful bacteria, thus starving them.



Unhealthful Bacteria
Lactobacillus acidophilus
Bifidobacteria
Fructooligosaccharides

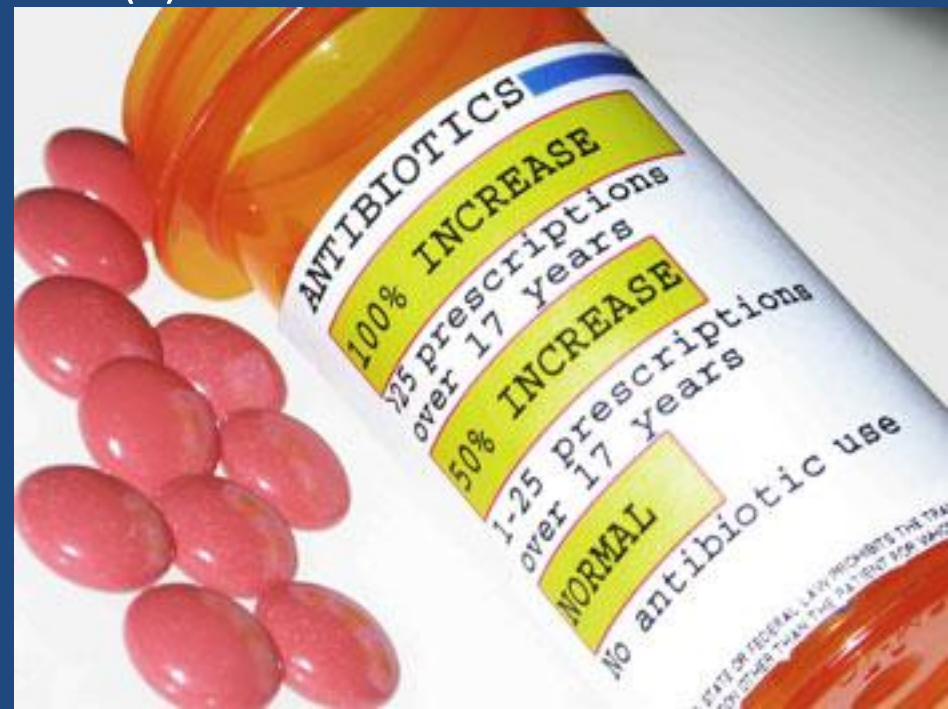
Toxins being detoxified

Yeast
Intestinal Deterioration
Toxins
Parasites

Antibiotics and Breast Cancer

- 17 year period -
 - > 25 scripts -- 2 x increased risk
 - 1-25 scripts --- 1.5 x increased risk
 - Int. J Cancer 2008. Nov 1: 123(9):2152-5.

- Immune system ?
- Damage to Gut



Heal The Gut

- Limit Antibiotic Use
- High Fiber Diet
- Decrease Red meat - <18 oz/wk (AICR)
- Probiotics
- Nutrients
- Remove inflammatory foods
- Treat infections



Increase Inflammation = Increase Cancer

Coussens LM, Werb. Inflammation and Cancer. *Nature* 2002; 420:860-7.



Signs of Inflammation

Increased CRP

Increased ESR

Water retention

Bloating

Joint Pain

Asthma

Eczema

Digestive Distress

Abdominal weight gain...

hsCRP

- hsCRP is a better marker than stage of disease
- < 1.0 40% alive after 3 years
- >1.0 none survived

- Associated with increased angiogenesis, invasion, metastasis

- McMillan DC, etal. Nutr Cancer. 2001;41(1-2):64-69.

Baseline C-Reactive Protein Is Associated With Incident Cancer and Survival in Patients With Cancer

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version. Use Adobe® Reader®.

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0732-183X/09/2713-2217/\$20.00

DOI: 10.1200/JCO.2008.19.8440

ABSTRACT

Purpose

We tested the hypothesis that baseline plasma levels of C-reactive protein (CRP) are associated with risk of incident cancer in the general population and early death in patients with cancer.

Patients and Methods

A total of 10,408 individuals from the Danish general population who had CRP measured at baseline were observed for up to 16 years; 1,624 developed cancer, and of these, 998 patients died during follow-up. We tested the hypothesis that elevated CRP is associated with diagnosis at baseline.

Results

Baseline CRP levels were associated with incident cancer. Adjusted hazard ratios (HRs) for lung cancer, 1.9 (95% CI, 1.1 to 3.1); colorectal cancer, 1.3 (95% CI, 0.5 to 1.7); and early death in patients with cancer, 1.8 (95% CI, 1.1 to 1.7) for the interaction; $P = .03$.

Conclusion

Elevated levels of CRP are associated with incident cancer of any type, of lung cancer, and colorectal cancer. CRP associates with early death in patients without metastases.

J Clin Oncol 27:2217-2224.

INTRODUCTION

C-reactive protein (CRP) is a marker of inflammation that is elevated during infectious disease, trauma, and cancer.¹ CRP is produced by the liver in response to elevated cytokines, which are released by cells in response to a stimulus.² Two hypotheses have been proposed to explain the relationship between elevated CRP levels and cancer.³ The first hypothesis states that elevated CRP levels are a result of an underlying cancer or a premalignant state, whereas the second hypothesis states that chronic inflammation and elevated CRP might have a causal role in carcinogenesis.

Case-control studies have reported higher levels of CRP in patients with cancer compared with controls,³ whereas results from prospective studies are conflicting, with some studies suggesting that CRP is not merely a marker of prevalent cancer, but

poor survival in patients with cancer.^{4,5,6,7,8,9} However, in only two of these studies including few participants were CRP measured with a high-sensitivity assay,^{7,10} allowing examination of associations in the high-normal interval just greater than 1 mg/L. Thus it is still unclear whether, and to which extent, CRP levels are associated with incident cancer as well as early death in patients with cancer.

We tested the hypothesis that baseline plasma levels of CRP in the general population are associated with risk of incident cancer, including the three

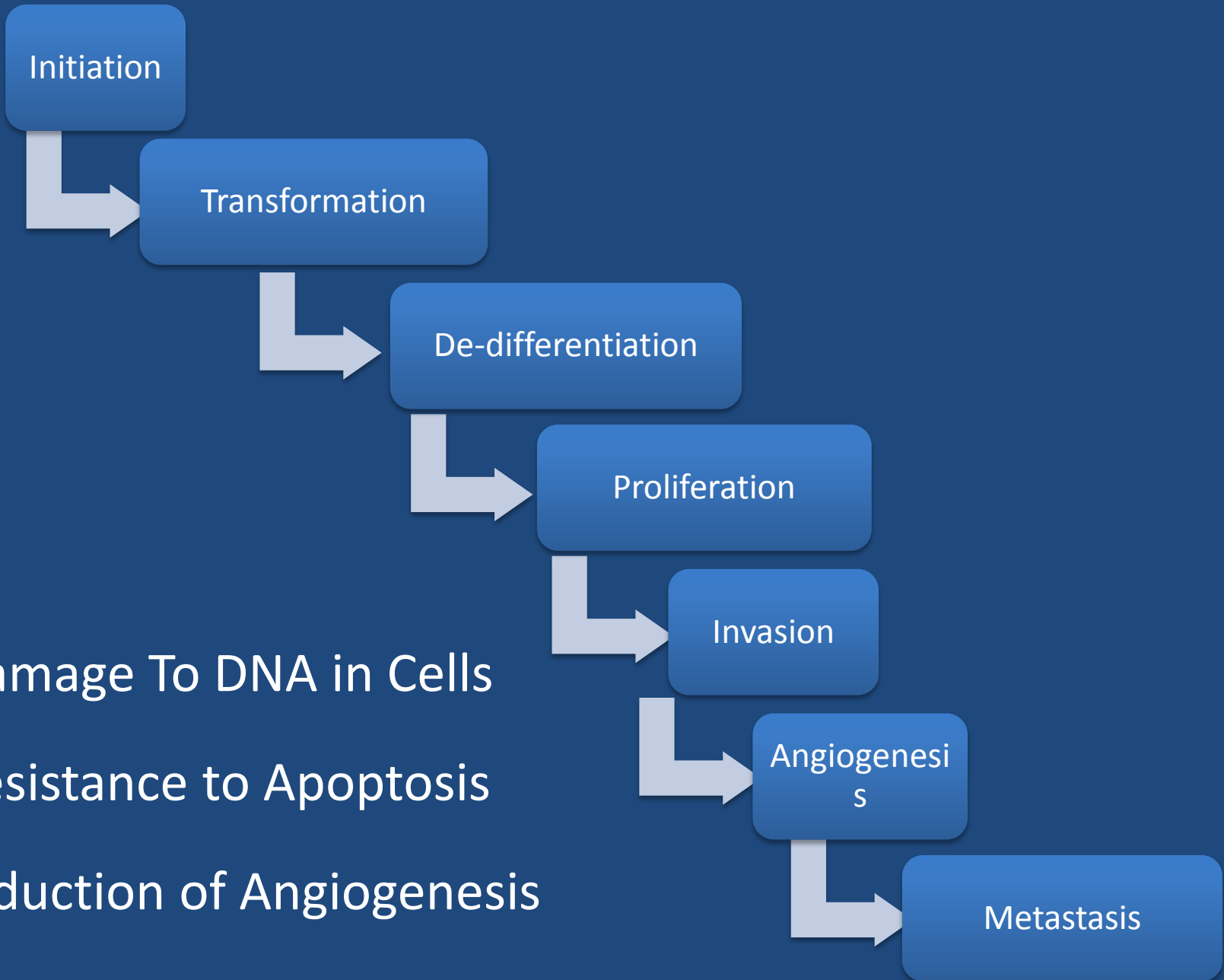
Elevated levels of CRP in cancer-free individuals are associated with increased risk of cancer of any type, of lung cancer, and possibly of colorectal cancer. Moreover, elevated levels of baseline CRP associate with early death after a diagnosis of any cancer, particularly in patients without metastases.

J Clin Oncol 27:2217-2224. © 2009 by American Society of Clinical Oncology

Chronic Inflammation: A Common and Important Factor in the Pathogenesis of Neoplasia

Recurrent or persistent inflammation may induce, promote, or influence susceptibility to carcinogenesis by causing DNA damage, inciting tissue reparative proliferation, and/or creating a stromal “soil” that is enriched with cytokines and growth factors. Future research on the complex cascade of cellular and humoral factors participating in the chronic inflammatory process will further understanding of the pathogenesis of various cancers and potentially provide a rationale for targeted chemopreventive interventions.

David Schottenfeld, MD, MSc; Jennifer Beebe-Dimmer, PhD, MPH
CA Cancer J Clin 2006;56:69–83



STOP Progression To Cancer

- 30-50% of healthy women aged 40-50 premalignant microscopic breast tumors on autopsy.
 - Black WC, Welch HG. Advances in diagnostic imaging and overestimations of disease prevalence and the benefits of therapy. *N Engl J Med* 1993;328:1237-43.
- **Some tumors regress !**
- Unhealthy Soil:
 - high insulin, sugar, omega 6, IGF milk and meat
- Healthy Soil
 - Phytonutrients, low inflammation, high omega 3, green tea, beta glucans

Decrease Inflammation

- Avoid refined and processed foods
- Decrease % Body Fat
- Increase Omega 3 fats
- Decrease Omega 6 and saturated fats and eliminate trans fats
- Turmeric, resveratrol, ginger and green tea
- Decrease stress and increase sleep

Effects of a Weight Loss Intervention on Body Mass, Fitness, and Inflammatory Biomarkers in Overweight or Obese Breast Cancer Survivors

Bilg  Pakiz · Shirley W. Flatt · Wayne A. Bardwell · Cheryl L. Rock · Paul J. Mills

  The Author(s) 2011. This article is published with open access at Springerlink.com

Abstract

Background Obesity is characterized by chronic mild inflammation and may influence the risk and progression of cancer.

Purpose The current study is an exploratory analysis of the effect of a weight loss intervention that emphasized increased physical activity on inflammatory cytokines

(tumor necrosis factor- α [TNF- α], interleukin-6 [IL-6], interleukin-8 [IL-8], and vascular endothelial growth factor [VEGF]) at the end of the intervention in overweight or obese breast cancer survivors.

Methods Study participants ($n=25$) participated in a 16-week weight loss management program. The intervention emphasized increased physical activity and 16-week data were analyzed for changes in TNF- α , IL-6, IL-8, and VEGF.

Results Weight loss was significantly greater in the intervention group than in the control group ($P=0.001$). Paired t tests

revealed significant decreases in TNF- α ($P=0.001$), IL-6 ($P=0.001$), and IL-8 ($P=0.001$) in the intervention group compared to the control group. There were no significant changes in VEGF levels. Increased physical activity was associated with changes in IL-6 for participants in the intervention group ($P=0.001$).

B. Pakiz ( ) · S. W. Flatt · W. A. Bardwell · P. J. Mills
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Effects of a Weight Loss Intervention on Body Mass, Fitness, and Inflammatory Biomarkers in Overweight or Obese Breast Cancer Survivors
Favorable changes in cytokine levels were observed in association with weight loss in this exploratory study with overweight breast cancer survivors.

Pakiz B, Int J Behav Med 2011 Feb 11.

increasingly being recognized as a medical condition that is characterized by chronic mild inflammation [7]. Several

Phytonutrients



Phytonutrients - plant metabolites that defend against microbes

- Increase host defense against DNA damaging molecules. Reduce oncogenic potential of carcinogens.
- Organic has more phytochemicals -- Stress

– J Agric Food Chem, 2009;57:5227-34.

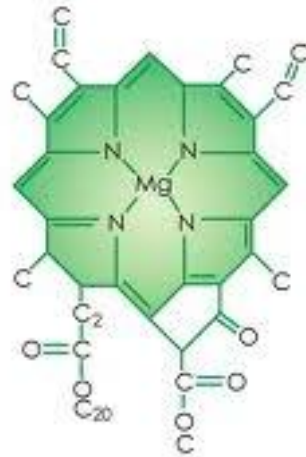
8 - 10 1/2 cups per day



Phytonutrients

- Chlorophyll – green vegetables
- Glucosinolates – cruciferous vegetables
- Xanthophyll – yellow carotenoid pigment
- Isoflavones – phytoestrogen
- Polyphenols – quercetin, lignan, flavonoids
- Flavonoids – Catechins, ECGC = epigallocatechin
- Carotenoids – yellow / orange

Chlorophyll



Plant Chlorophyll



Glucosinolates

- Cruciferous vegetable - Give bitter taste
- Pro apoptotic activity
- Estrogen metabolism



Isoflavones

- Phytoestrogens
- Genistein
- Daidzein
- Soy



Soy Food Intake and Breast Cancer Survival

Xiao Ou Shu, MD, PhD

Ying Zheng, MD, MSc

Hui Cai, MD, PhD

Kai Gu, MD

Zhi Chen, MD, PhD

Wei Zheng, MD, PhD

Wei Lu, MD, PhD

ESTROGEN IS BELIEVED TO PLAY a central role in breast cancer development and progression. Blocking the effect of estrogen, either by inhibiting estrogen action or by reducing estrogen production, has been widely used in breast cancer treatment as an adjuvant therapy.¹ Soy foods are rich in phytoestrogens, mainly in the form of isoflavones, which are natural estrogen receptor modulators that possess both estrogen-like and antiestrogenic properties. Soy constituents have also been shown to have other anticancer effects, including the inhibition of DNA topoisomerase I and II, proteases, tyrosine kinases, inositol phosphate, and angiogenesis and may also boost immune response and possess antioxidative effects.^{2,3}

Consumption of soy food has been inversely related to the risk of breast cancer in many epidemiological studies.⁴⁻⁶ However, genistein, a major form of isoflavone, has been shown to enhance the proliferation of breast cancer cells in vitro and to promote estrogen-dependent mammary tumor growth in ovariectomized rats.^{3,7} In addition, breast cancer treatments often lead to a decrease in the endogenous estrogen supply of survivors, and a concern has been raised as to whether soy isoflavones may exert their estrogenic effects, promote cancer recurrence, and, thus, negatively influence overall survival.^{7,8} Furthermore,

For editorial comment see p 2483.

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Context Soy foods are rich in isoflavones, a major group of phytoestrogens that have been hypothesized to reduce the risk of breast cancer. However, the estrogen-like effect of isoflavones led to concern.

Objective Cancer with

Design, S

large, population-based cohort study of 5042 female breast cancer survivors in China. Women aged 20 to 75 years with diagnoses between March 2002 and April 2006 diagnosis a gression and was re after diagn tabase was follow-up.

Main Out cancer-rel known clin time-depen

Results and 534 re treated bre isoflavone i associated v al [CI], 0.5 pared with were 10.3% tively, for v association tive breast

Conclusio cantly asso JAMA. 2009;

both in viv gested tha with tamot ic and an been repoi

To our l logical stu demiology ated the as isoflavone rence. An gested for had used

The Shanghai Breast Cancer Survival Study

Among women with breast cancer, soy food consumption was significantly associated with **decreased risk of death and recurrence.**

The inverse association was evident among women with either ER-positive or ER-negative breast cancer and was present in both users and non-users of tamoxifen.

This study suggests that moderate soy food intake is **safe and potentially beneficial** for women with breast cancer.

Shu, X. JAMA, 2009;302:2437-43.

Flavonoids

- Anthocyanidins = Berries (Red, blue and purple)
- ECGC – Epigallocatechin – green tea
- Flavonols = onion and kale



Antiangiogenic properties of natural polyphenols from red wine and green tea.

In vitro investigations have indicated that RWPCs (red wine polyphenolic components) and GTPs (green tea polyphenols) are able to **inhibit several key events of the angiogenic process**



STRESS!



STRESS – Increased Cortisol

- Increased insulin resistance and abdominal fat
- Increased IL-6 - inflammatory cytokine
 - Increased Inflammation = Increase Cancer Risk
- Lower NK (natural killer) cell activity
 - NK cells find and kill new cancer cells
 - Stronger a women's NK cell activity is the higher rate of survival from breast cancer after 12 years
 - Head JF. Assessment of Immunologic Competence and Host Reactivity Against Tumor Antigens In Breast Cancer Patients. *Annals of the NY Acad of Sciences*, 1993; 690:340-42.
 - Increased Social Support = Increased NK activity

Tumor rejection in rats after inescapable or escapable shock.

Visintainer, M Science, 1982; 216: 437-439.

- Rats with cancer cells grafted to cause 50% to die
- 3 groups
- Shock and no control - 27% rejected tumor
- No electric shock - 54% rejected tumor
- Electric shock but had a lever to stop it
 - 63% rejected the tumor





Sleep

SLEEP DEPRIVATION



Cortisol and Insulin

NK cells and melatonin

Melatonin = Anticancer and antioxidant effects

EXERCISE



Exercise and Breast Cancer

- 4 hrs per week = less risk
- 3-5 hours per week = improved survival for women who have had breast cancer
- Vigorous exercise + BMI < 25
– 20% decreased risk

JAMA – 2005
Breast Ca Research 2008



DIET



- Reduced calorie diets = reduced risk
 - Oxidative Stress
- High fiber, low fat diets = decreased estrogen in body
- High fat diet - increased reoccurrence ER- cancer

WINS - Women Intervention Nutrition Study

- Soy in adolescents = lower risk
- Green tea - ECGC - anti-angiogenesis and antioxidant



Supplements

- Vitamin D -
 - 25OH vit D > 52 = 50% decreased risk breast cancer than if vit D <12ng/dl
 - Garland etal. AACR 2006
- Probiotic
- DIM / I3C
- Sulforaphane
- Calcium d glucurate
- Fish oil – 1000mg EPA + DHA
- B vitamins

1/3rd of all cancers can be prevented...at least!

- Exercising Regularly
- Eating Healthy Foods with Increased Fruits and Vegetables
- Maintaining a Healthy Weight
 - Decrease breast cancer by 38%
- Policy and Action for Cancer Prevention - Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective. 2007 WCRF / AICR

Government Role

- Increase Availability of Farmer's Markets
- Increase Bike Lanes and Walking Paths
- Get Rid of Vending Machines in Schools
- End Advertising of Junk Food To Kids
- Take High Fructose Corn Syrup out of products
- Ban Trans Fats
- Decrease toxic chemicals allowed in our environment.



What Can We Do?

- Choose Whole Foods
- Get 3-5 hours of Exercise Per Week
- Increase Fiber Intake to 35gm daily
- Have Protein at Every Meal - include vegetarian options - beans, nuts as well as fish, lean poultry and eggs.
- Maintain a Healthy Weight



What Can We Do?

- Get a Good Night Sleep
- Choose Organic Foods
- Avoid Excess Toxins
- Take Probiotics
- Limit Your Alcohol Intake
 - <1 drink per day or 5 per week.



THANK YOU !

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