What are Natural Cancer Vaccines - *and have we missed 'em?*

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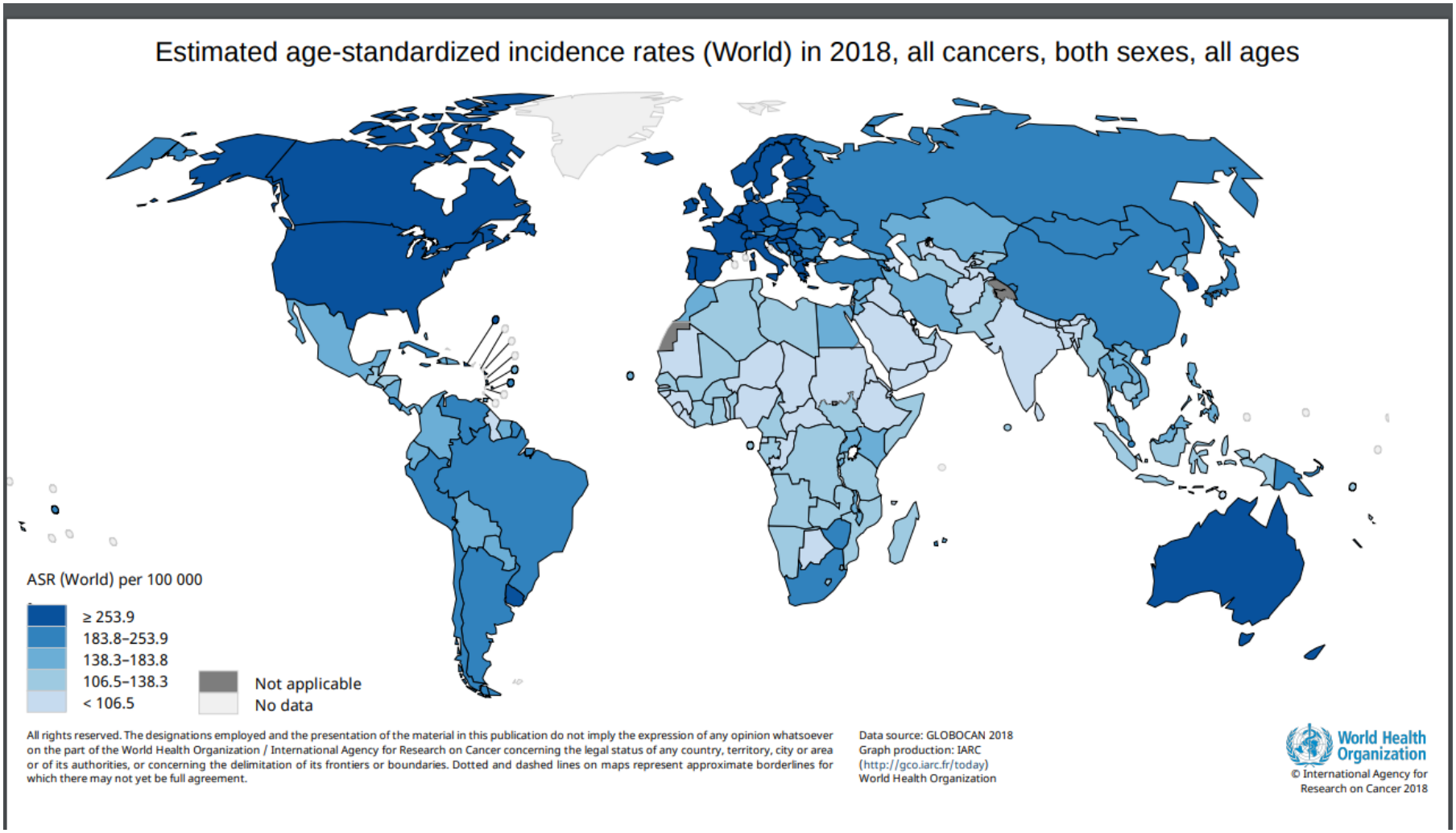
World Cancer Burden 2018



Source Globocan

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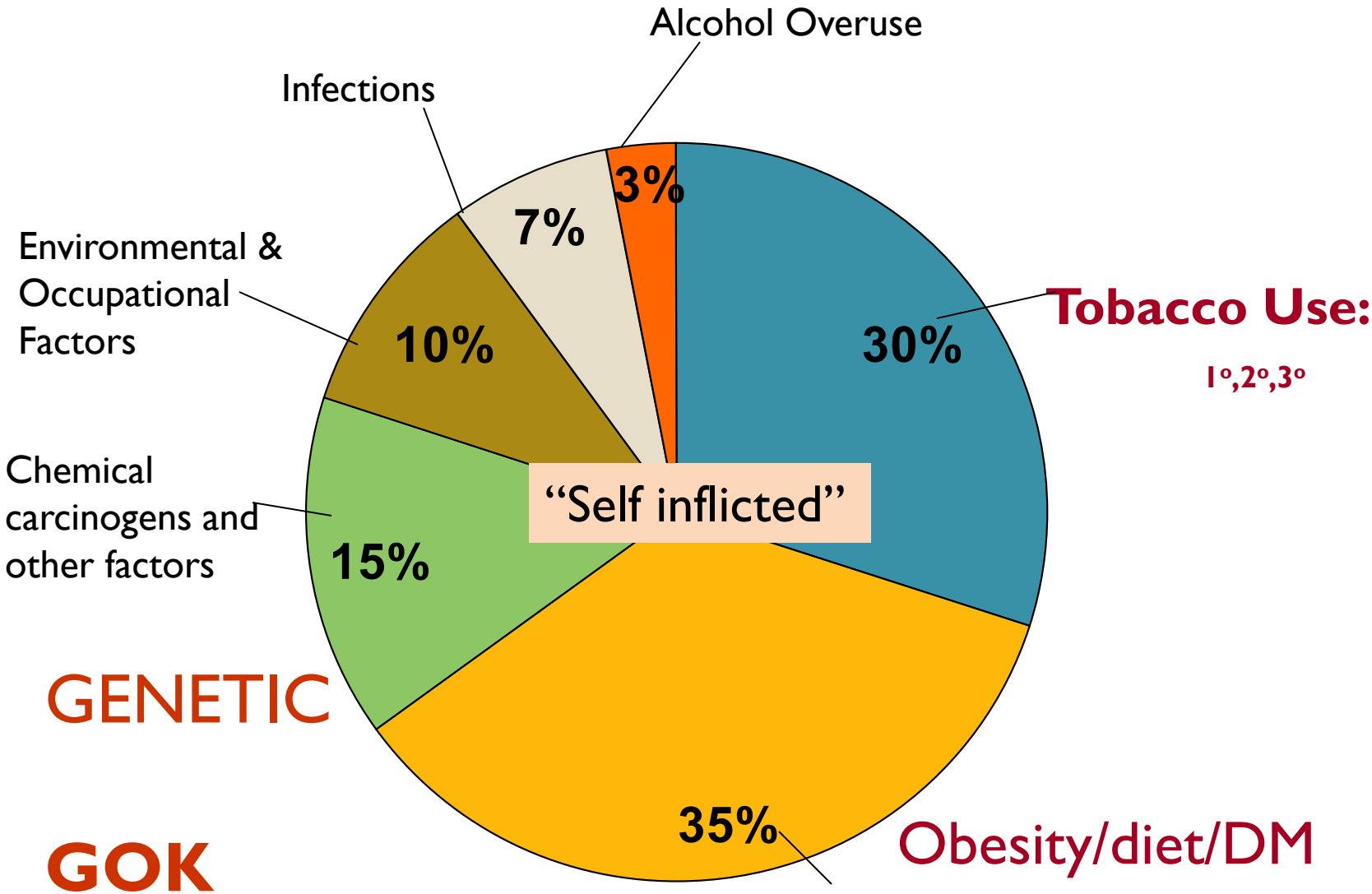
How and why people get cancer?

Risk Factors For Cancer Development



Diabetes and cancer

Table 1 Meta-analyses on the relative risk (RR) of cancer in different organs of diabetic patients

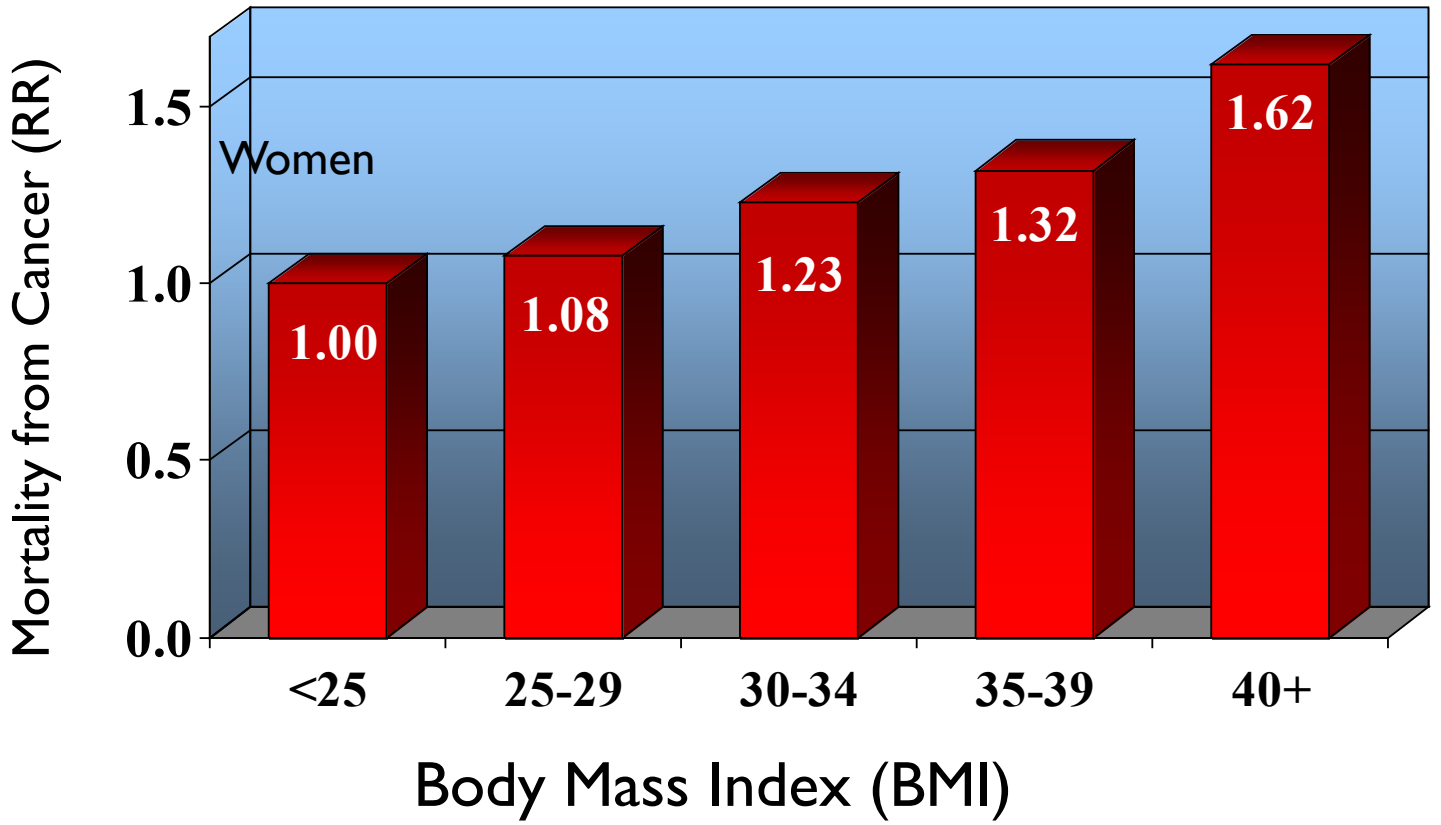
Cancer		RR (95% CI)
Liver (El-Serag *et al.* 2006)	13 case–control studies	2.50 (1.8–3.5)
	7 cohort studies	2.51 (1.9–3.2)
Pancreas (Huxley *et al.* 2005)	17 case–control studies	1.94 (1.53–2.46)
	19 cohort studies	1.73 (1.59–1.88)
Kidney[a] (Lindblad *et al.* 1999, Washio *et al.* 2007)	1 cohort study	1.50 (1.30–1.70)
	1 cohort study	2.22 (1.04–4.70)
Endometrium (Friberg *et al.* 2007)	13 case–control studies	2.22 (1.80–2.74)
	3 cohort studies	1.62 (1.21–2.16)
Colon–rectum (Larsson *et al.* 2005)	6 case–control studies	1.36 (1.23–1.50)
	9 cohort studies	1.29 (1.16–1.43)
Bladder (Larsson *et al.* 2006)	7 case–control studies	1.37 (1.04–1.80)
	3 cohort studies	1.43 (1.18–1.74)
Non-Hodgkin's lymphoma (Mitri *et al.* 2008)	5 cohort studies	1.41 (1.07–1.88)
	11 case–control studies	1.12 (0.95–1.31)
Breast (Larsson *et al.* 2007)	5 case–control studies	1.18 (1.05–1.32)
	15 cohort studies	1.20 (1.11–1.30)
Prostate (Kasper & Giovannucci 2006)	9 case–control studies	0.89 (0.72–1.11)
	10 cohort studies	0.81 (0.71–0.92)

[a]Data on kidney cancer were not obtained from meta-analysis.

Vigneri et al; Endocrine-Related Cancer (2009) 16, 1103–1123

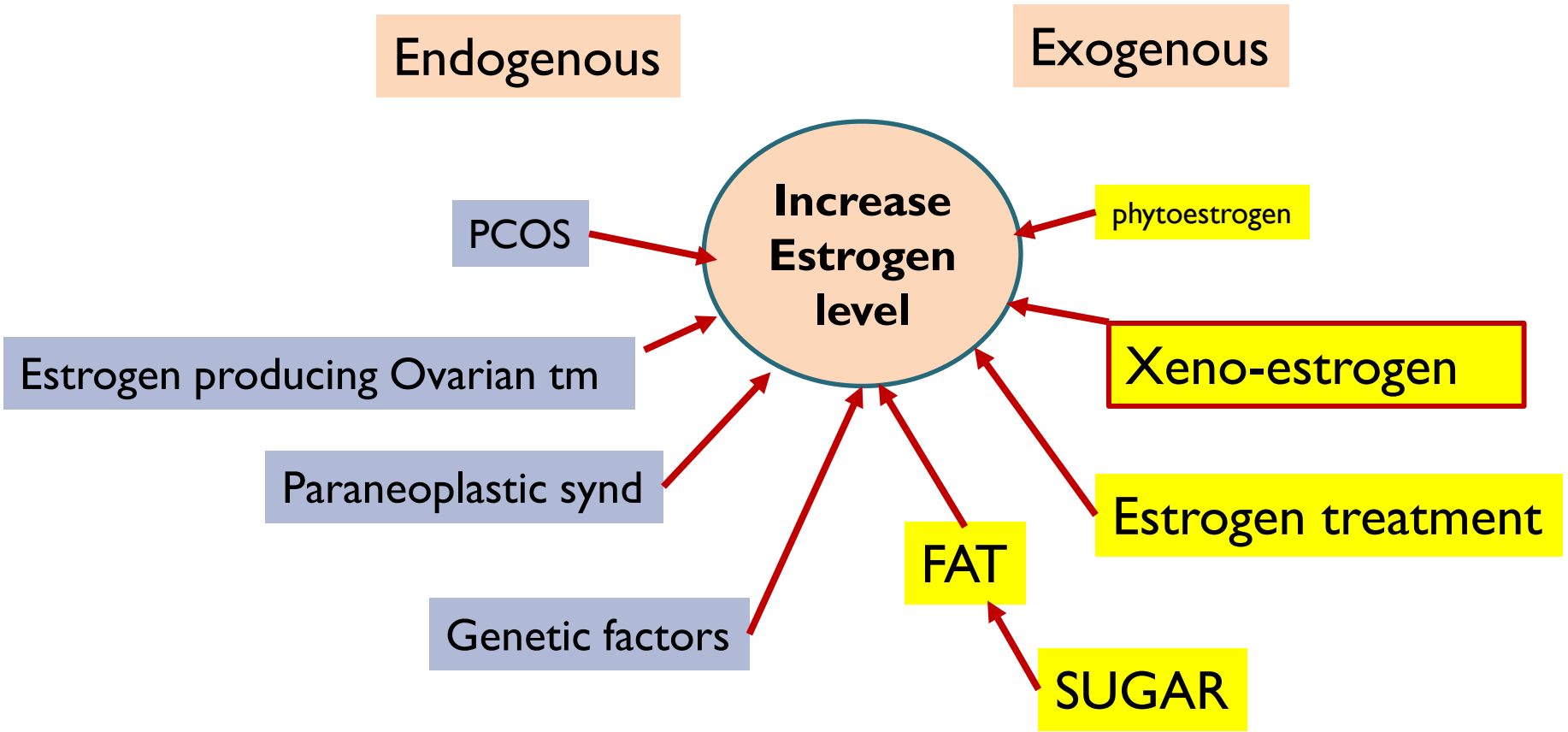
Obesity and Cancer Risk

n=495,477
16 yr study

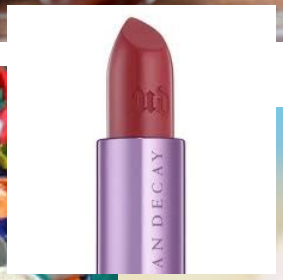


New England Journal of Medicine, Apr 24, 2003

For ladies – beware of Estrogen!



Some examples…



Estrogen related ca: Breasts, Endometrium, Ovaries, Colorectum, Meningioma etc…

Are there natural cancer vaccine?

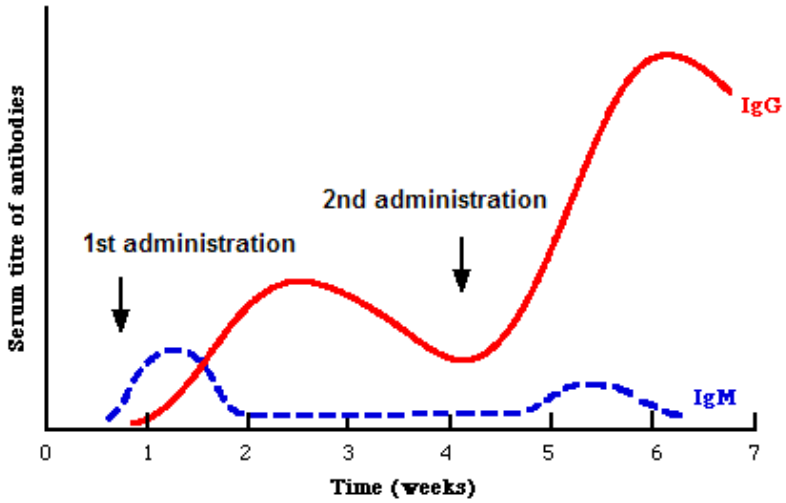
What is a Vaccine?

- A *product* which produces *immunity* therefore protecting the body from the *disease*
- A vaccine can be **preventive**, **therapeutic**, or both
- Synthetic vaccines
- Natural vaccines

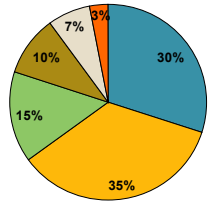
Boosters

- For most vaccines, the immunity against a particular pathogen has a tendency to wear off over time.

- In this case, a periodic "booster" administration must be given in order to strengthen and lengthen the duration of immunity.



Vaccine 1: Reduce Risk Factor

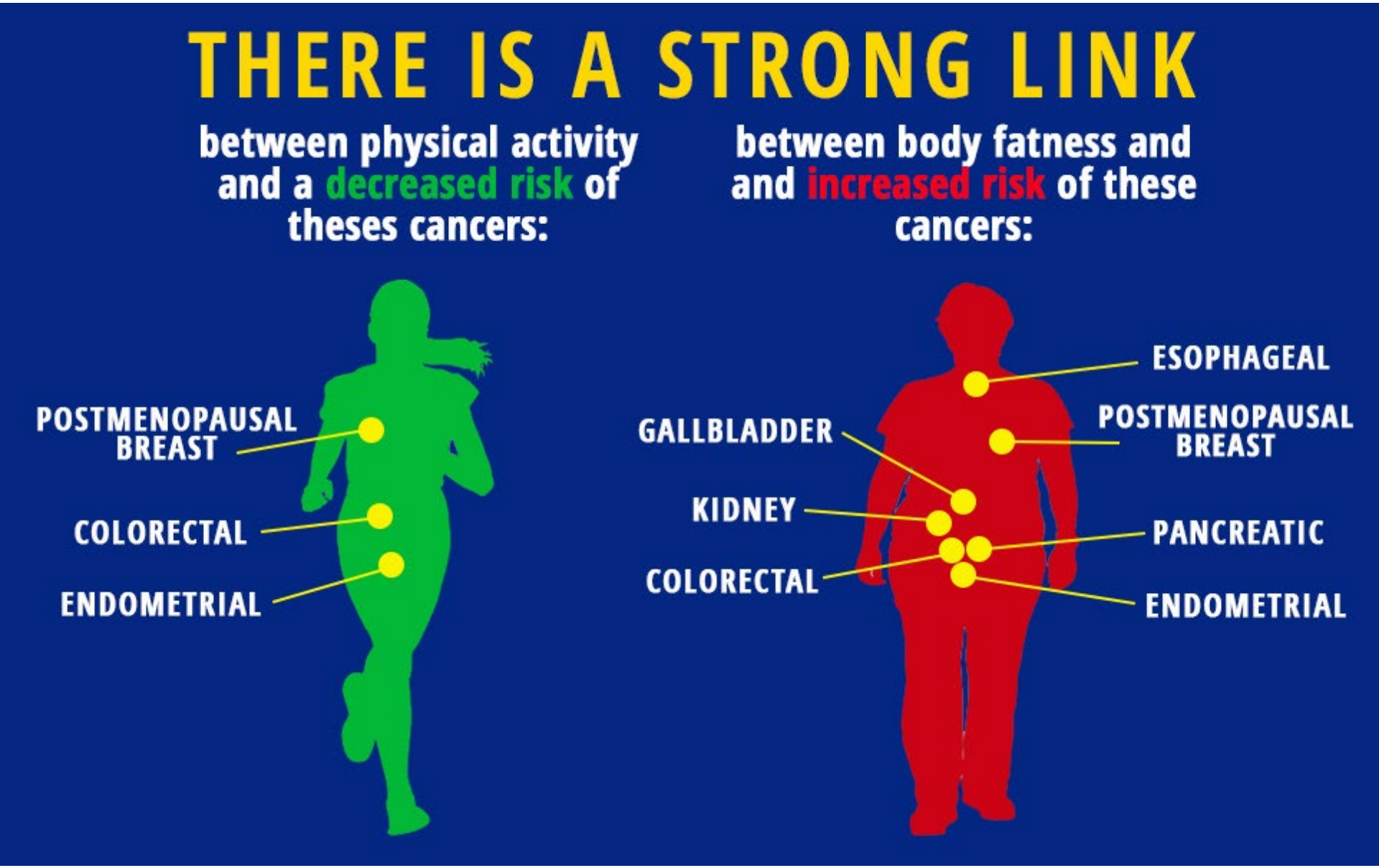


- Prevention is better than cure
- Almost impossible
  - Kick out smokers from your vicinity
  - Check-in in non-smoking rooms
  - Read mantra "*White sugar is poison*!"
  - Mind over matter

Vaccine 2: Exercise; 30/7/7

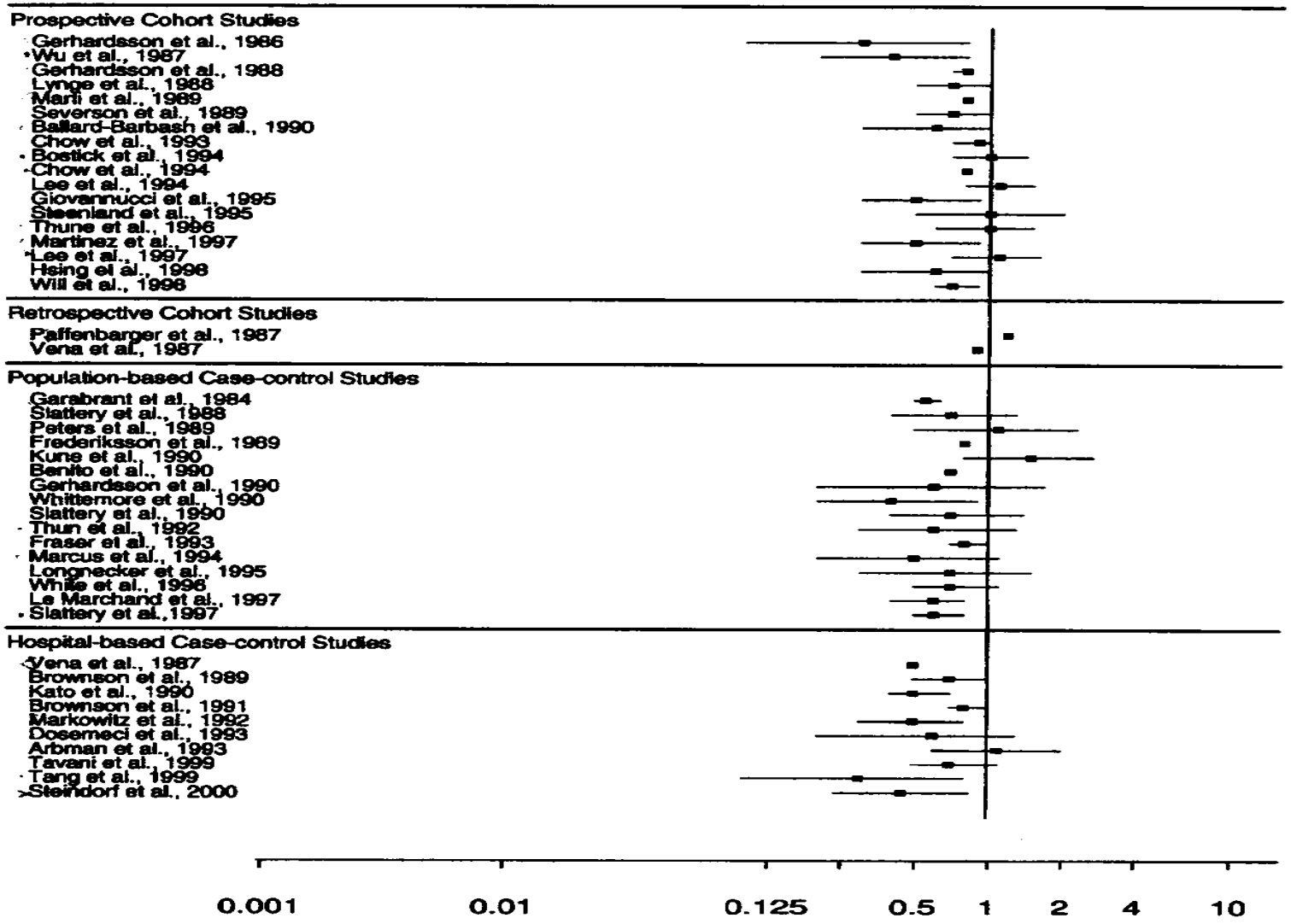
- Very potent vaccine

Fitness Vs Fatness



Evidence that exercise ‘protects’ against cancer development

Physical Activity and Colorectal Cancer Risk



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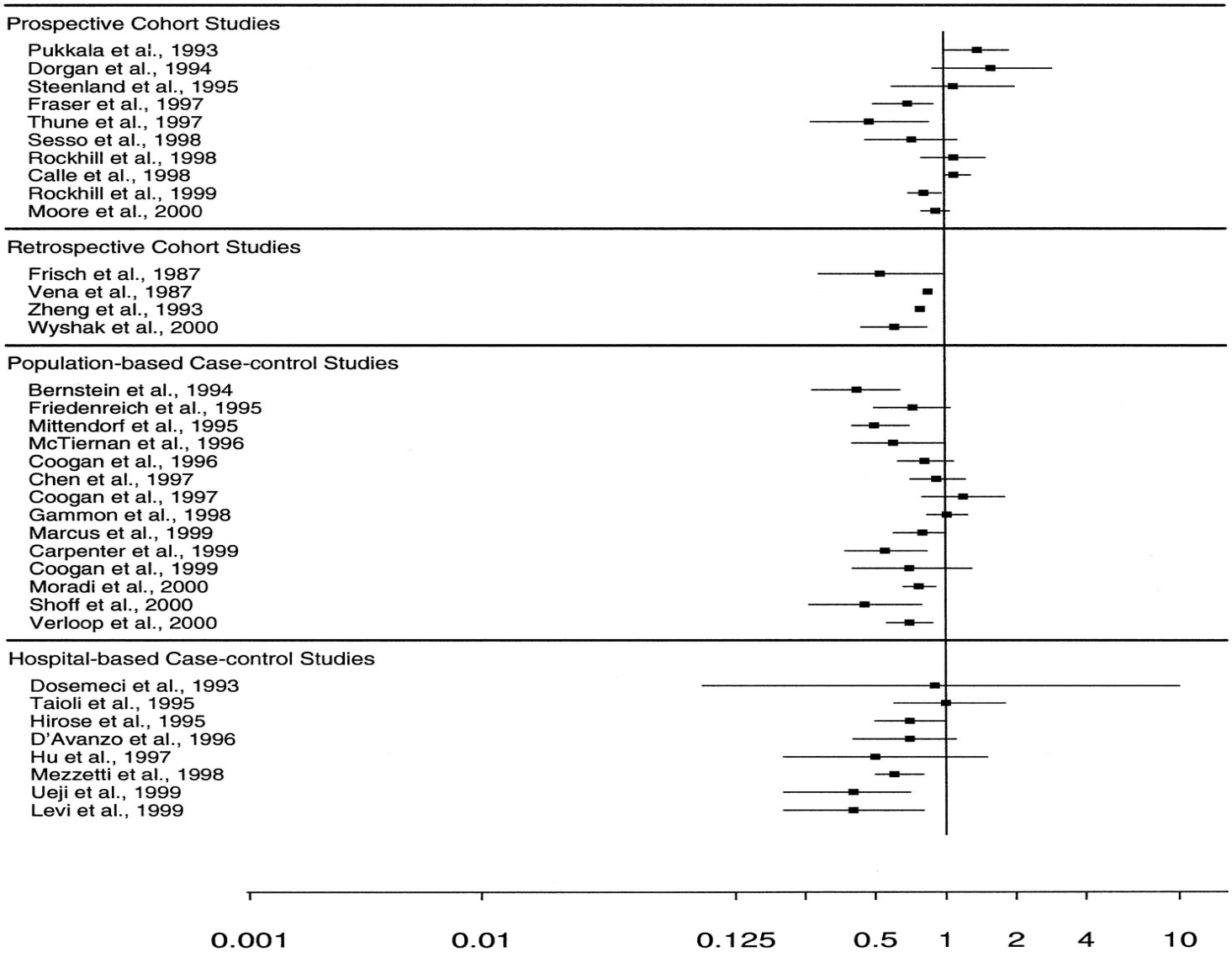
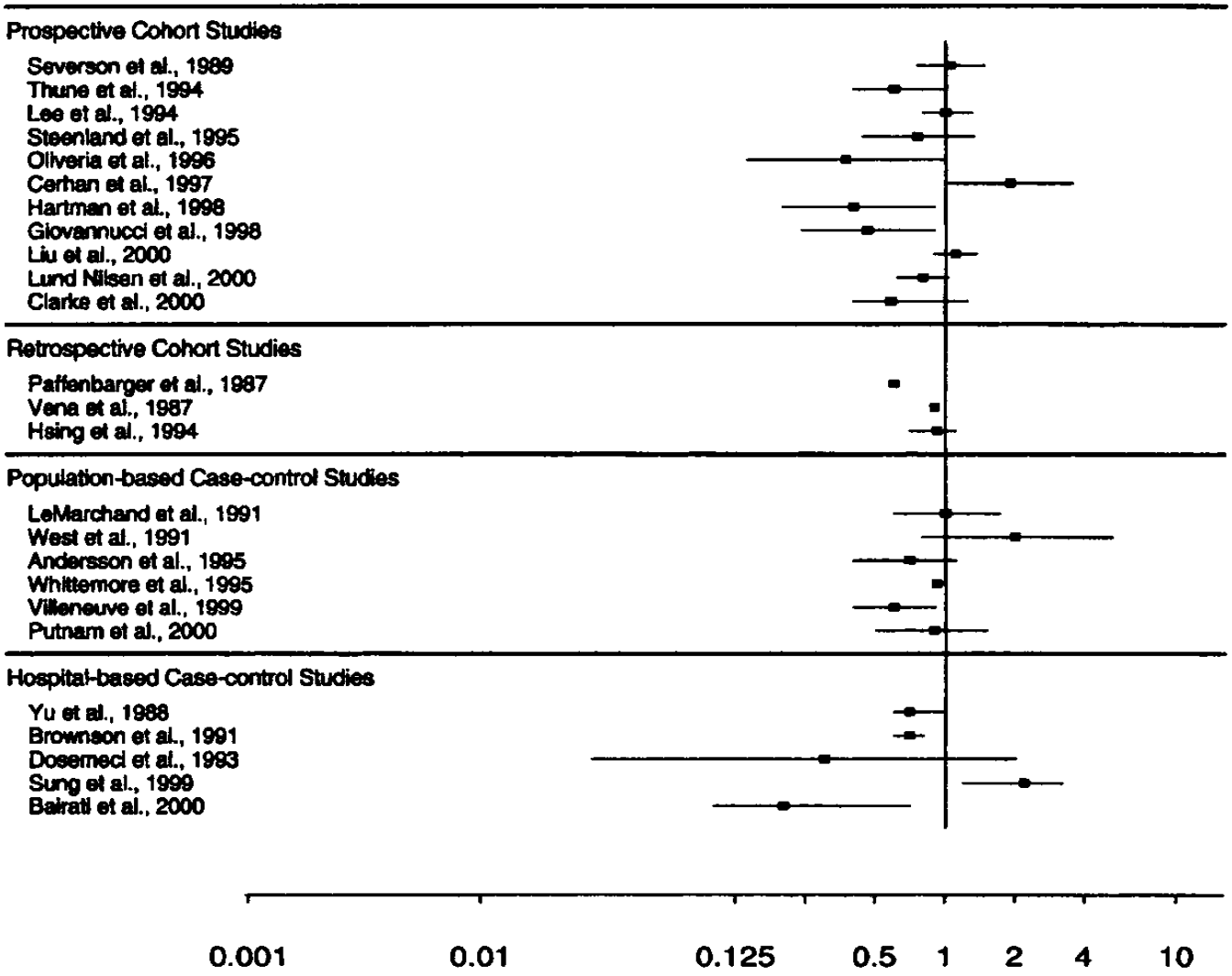
Physical Activity and Breast Cancer Risk

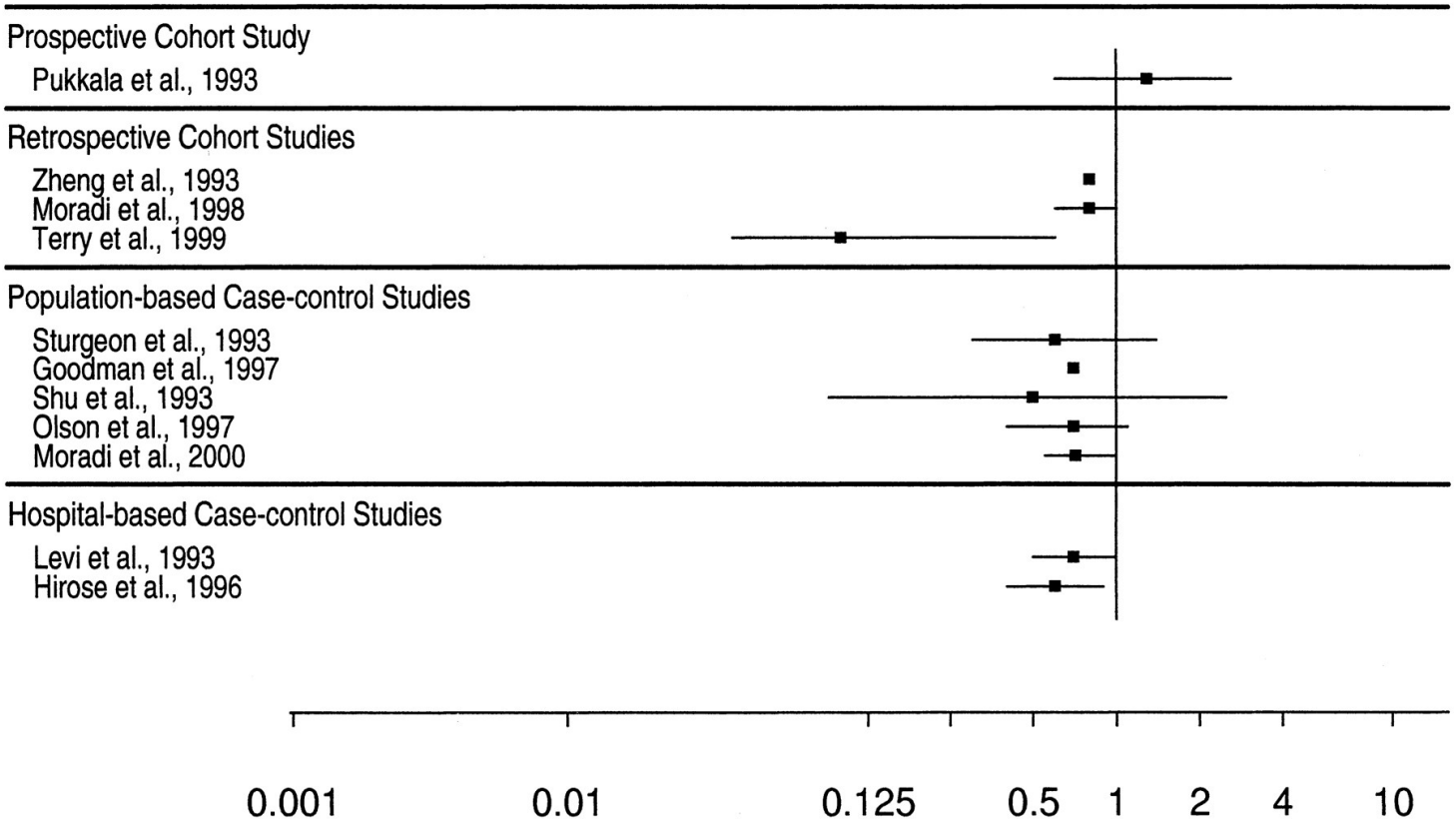


Physical Activity and Prostate Cancer Risk

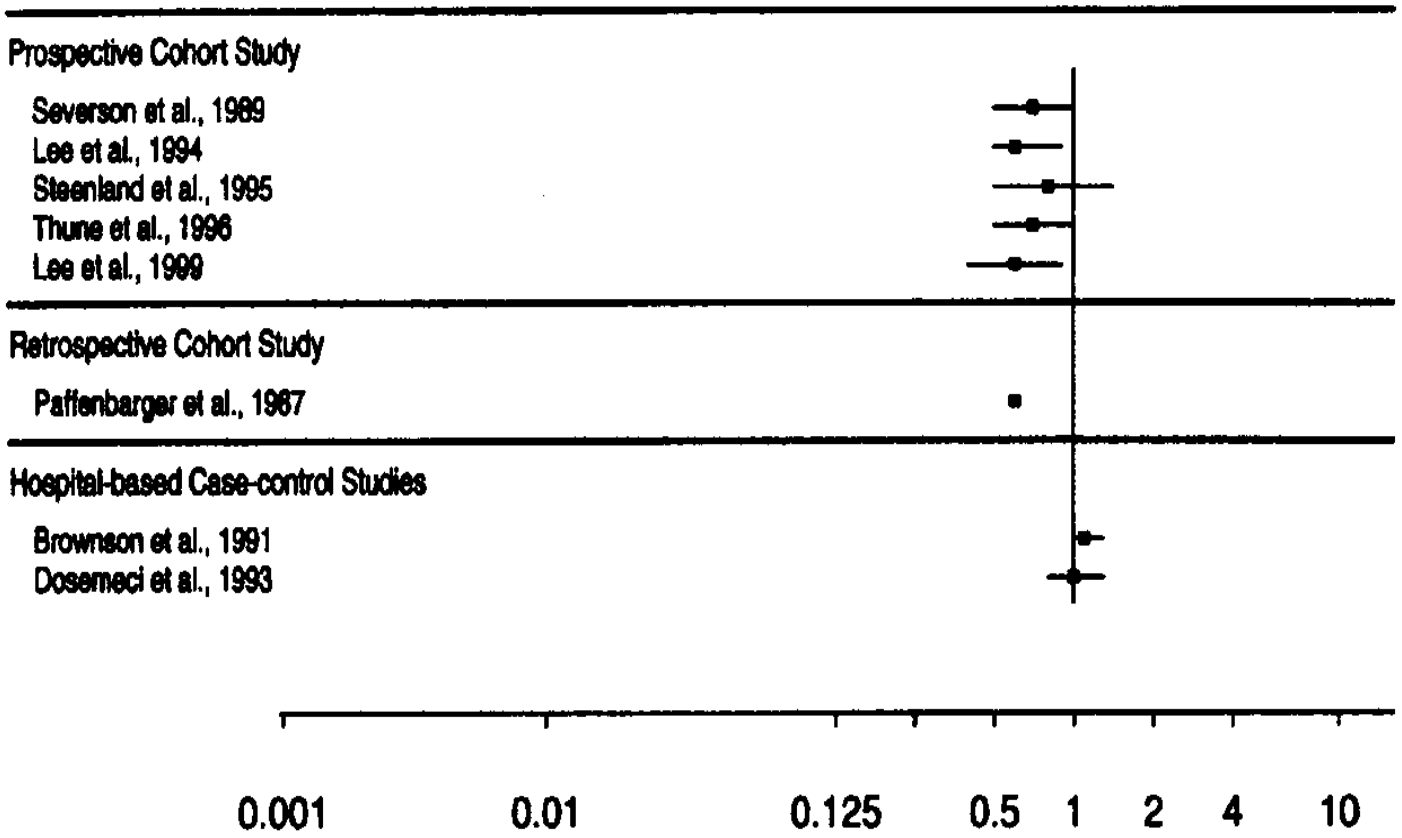


Freidenreich, Cancer Epid Biomark Prev, 10:287-301, 2001

Physical Activity and Endometrial Cancer Risk

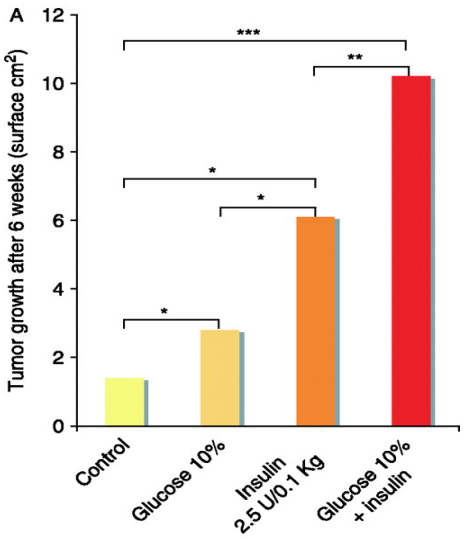


Physical Activity and Lung Cancer Risk

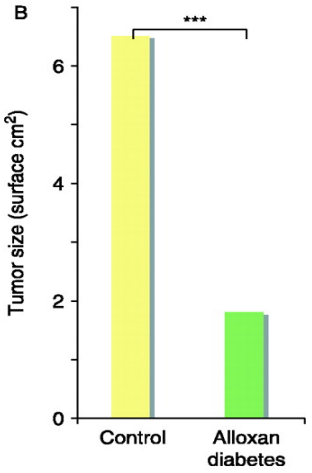


Freidenreich, Cancer Epid Biomark Prev, 10:287-301, 2001

VACCINE 3: WATCH WHAT YOU EAT



Mammary tumor growth in four matched groups of rats, given either normal diet or with the addition of oral glucose or of insulin injections or both (significant differences: *P<0.05; **P<0.01; ***P<0.0005; *Heuson et al. 1972*).



Mammary tumor regression after induction of alloxan diabetes in two groups of matched rats. Observation period=6 weeks; *P*<0.001 *Heuson et al. 1972*

Endocr Relat Cancer. 2009 Dec;16(4):1103-1123

Society for Endocrinology
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Stop or reduce taking
C.
Carbonated Drinks
R.
Refined Sugars
A.
Artificial Foods
P.
Processed Foods
100 Calorie
Goldfish

Bad vs good (cancer) diet type

- High sugar diet
- High fat, cholesterol, saturated fat
- High calorie
- Alcohol
- Preserved foods (pickles)
- Processed foods
- Iron overload [too much red meat]
- Vitamins and minerals deficiency

- Low sugar diet
- Low calorie
- Less fat
- Fresh
- Macronutrients
  - Fiber
  - omega-3 fatty acid
- Micronutrients
  - vitamins: A, D, E,C, B6, folic acid
  - minerals: Ca, Se, Zn, Mg

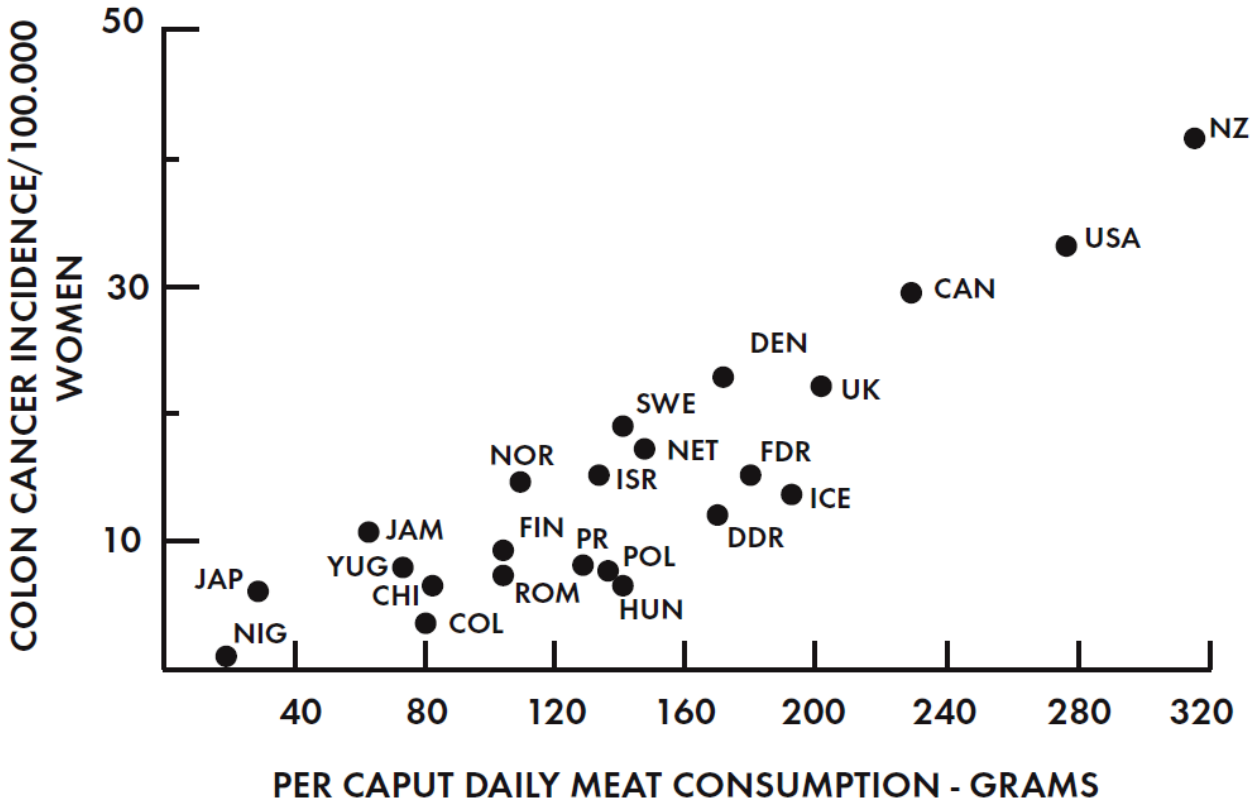
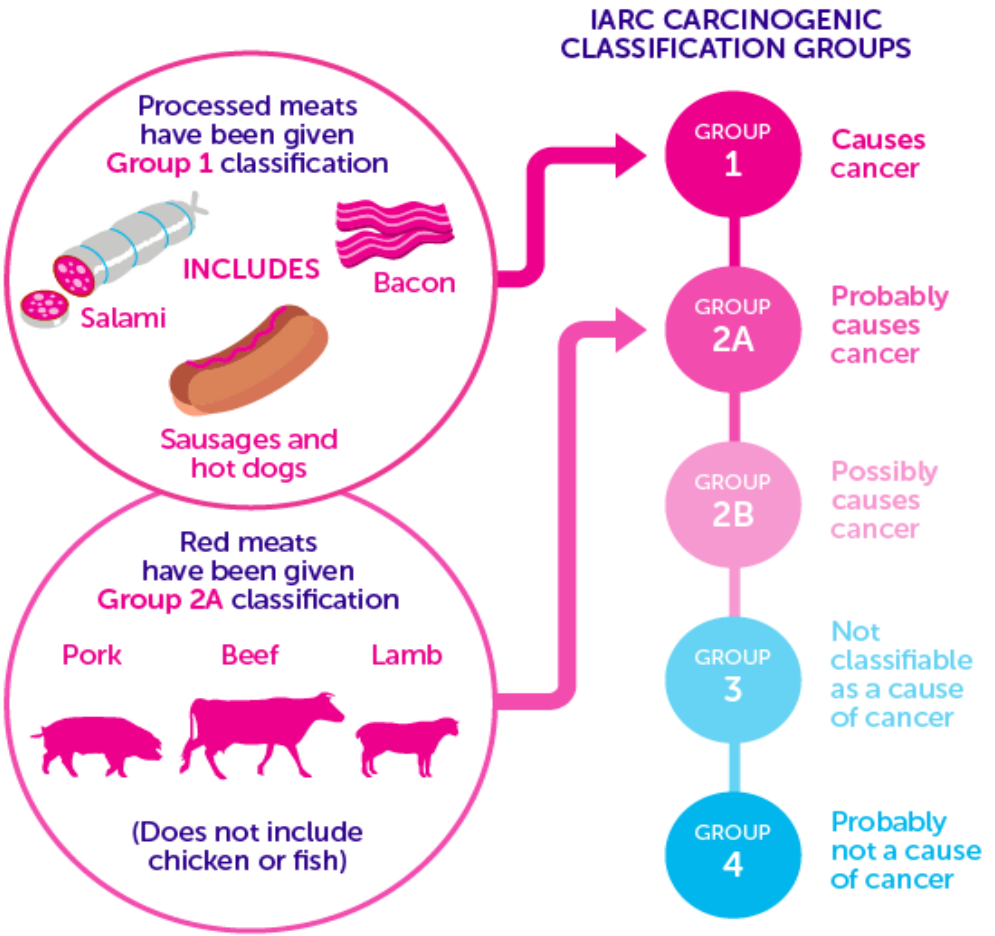


Fig. 2.9.1 *Correlation between incidence of colon cancer in women and mean individual daily meat consumption in 23 countries [6]*

Ref: World cancer Report 2008

MEAT AND CANCER
HOW STRONG IS THE EVIDENCE?



These categories represent how likely something is to cause cancer in humans, not how many cancers it causes.

WE WILL BEAT CANCER SOONER
cruk.org

CANCER RESEARCH UK

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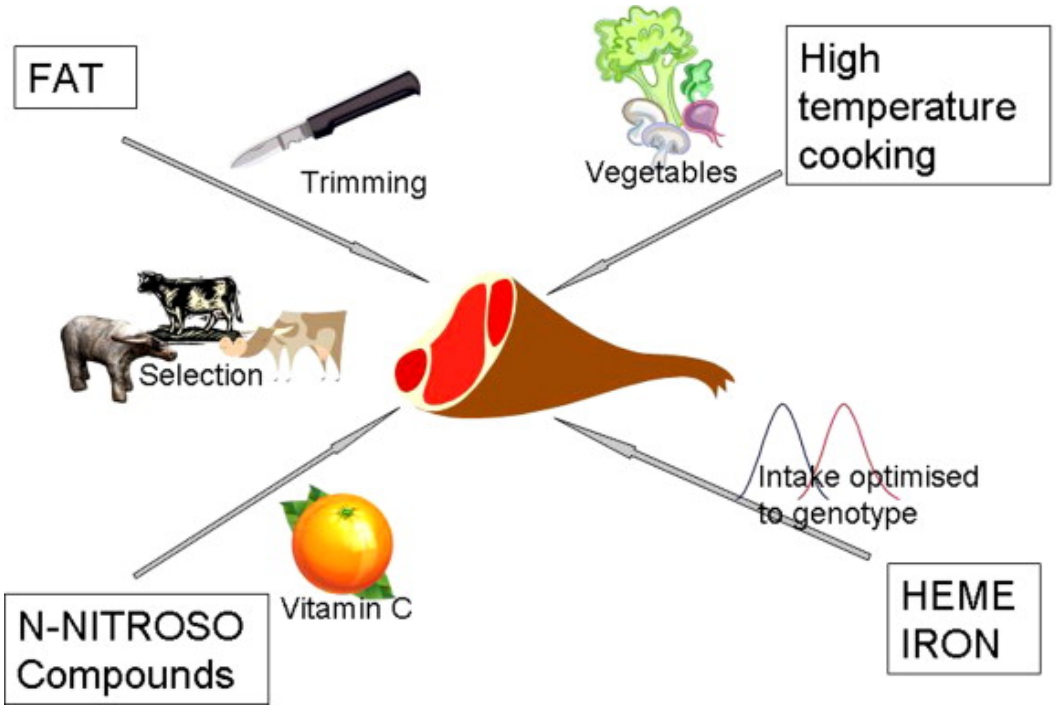
Possible approaches to reduce cancer risk:



- Trimming fat off meat.
- Eat meat with high intake of veges, fruits and cereals
- The efficacy of formation of free radicals is reduced by high levels of vitamins C or E.
- Reduce high overall dietary iron intake

Ref: Meat Science. Volume 84, Issue 2, February 2010, Pages 308–313

Fibre and Cancer

- Decrease intestinal transit time
- Decrease time for contact of carcinogens with the colonic tissue
- Dilute carcinogens and bile acids (Promoter of carcinogen) in the gut
- Change the bacterial flora and fermentation capability
- Too much fiber may itself injury the mucosa of the colon and enhance carcinogenesis

TOP CANCER CAUSING FOODS


Processed meats


Cookies


Hot dogs


French fries


Doughnuts


Crackers


Chips


Bacon

TOP ANTI CANCER FOODS

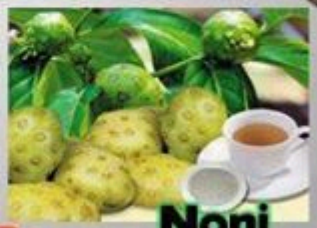
Leafy Green Vegetables


Cauliflower


Turmeric


Soursop


Broccoli sprouts


Noni


Tomatoes


Garlic

Vaccine 4: Natural Honey

Causes of cancer

Accumulation of toxic free radicals reactive oxygen species due to;
•Smoking; Alcohol; Obesity; diabetes, environmental factors etc..

Chronic infections; for e.g. bacteria (H.pylori), virus (HPV, EBV, Hep B, C), parasites (shistosomiasis), fungus (Aspergilus flavus)

Low immune status e.g due to diabetes, chronic illness, obesity

Chronic inflammation e.g colorectal carcinoma in Crohns disease and ulcerative collitis

Chronic non-healing ulcers e.g squamous cell carcinoma developing in chronic traumatic wounds

Genetic Inheritance

GOK

Compositions of honey

NUTRIENT:

Water

sugars

....Fructose

....Glucose

....Maltose

....Sucrose

Proteins, amino acids, vitamins and minerals

Vitamins

....Thiamin

....Riboflavin

....Niacin

....Pantothenic acid

....Pyridoxine (B^6)

....Ascorbic Acid (C)

Minerals

....Calcium

....Copper

....Iron

....Magnesium

....Manganese

....Phoshorus

....Potassium

....Sodium

....Zinc

high antioxidant activity

Phenolic

flavonols, flavavones, flavones, anthocyanidins isoflavones

-flavonoids

- Pinocembrin
- Pinobanksin
- chrysin,
- galangin,
- luteolin,
- quercetin
- Kaempferol
- Apigenin

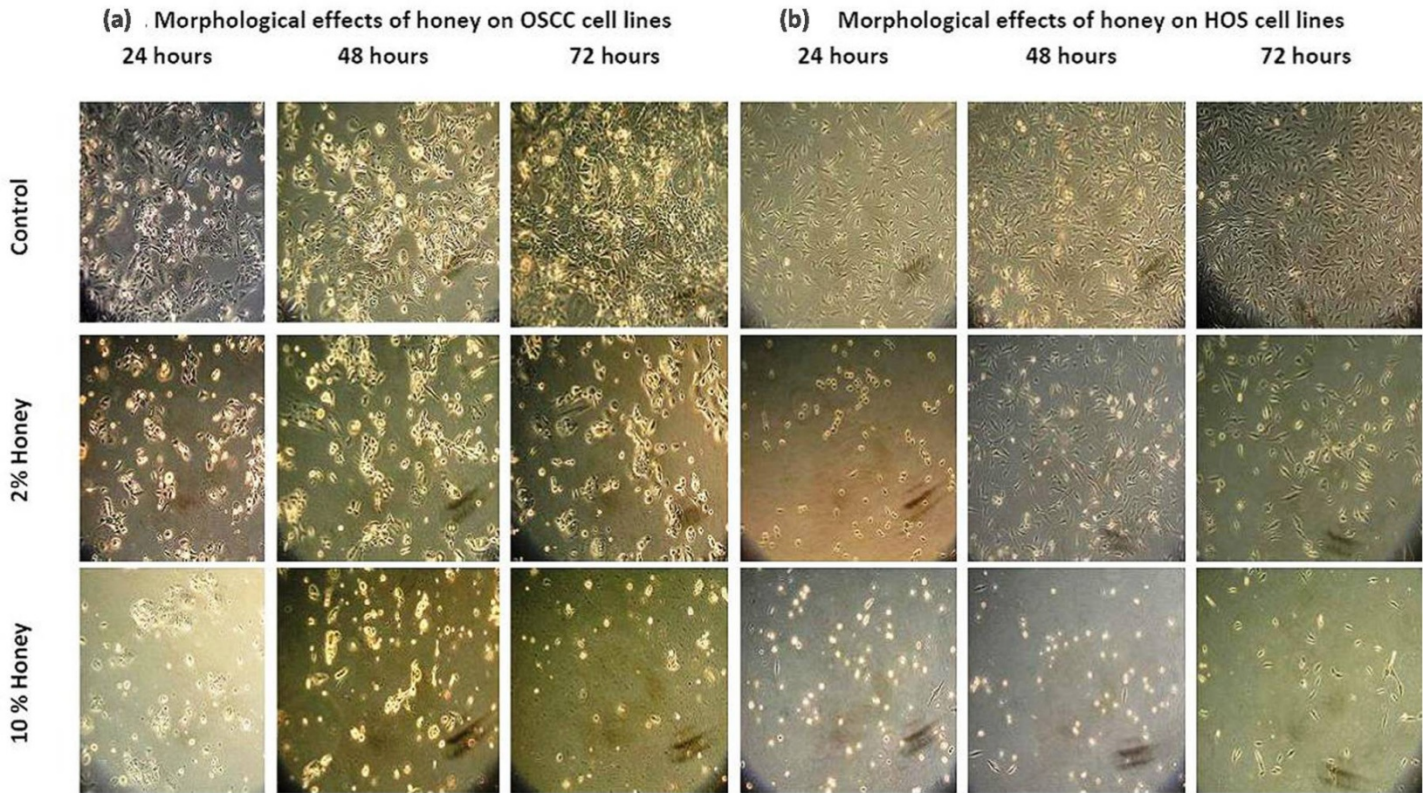
Why is honey good in preventing cancer?

Scientific evidence is growing:-

1. Honey – is a *natural immune booster*
2. Honey – is *natural anti-inflammatory agent*
3. Honey - is *natural antimicrobials*
4. Honey- is a 'fixer' for chronic ulcers and wounds
5. Honey – is possible agent for controlling obesity
6. Honey – is a possible *natural cancer 'vaccine'*
7. *Honey – has potential as cancer therapeutic agent*

Oral Sq cell carcinoma (OSCC)

Human Osteosarcoma (HOS)

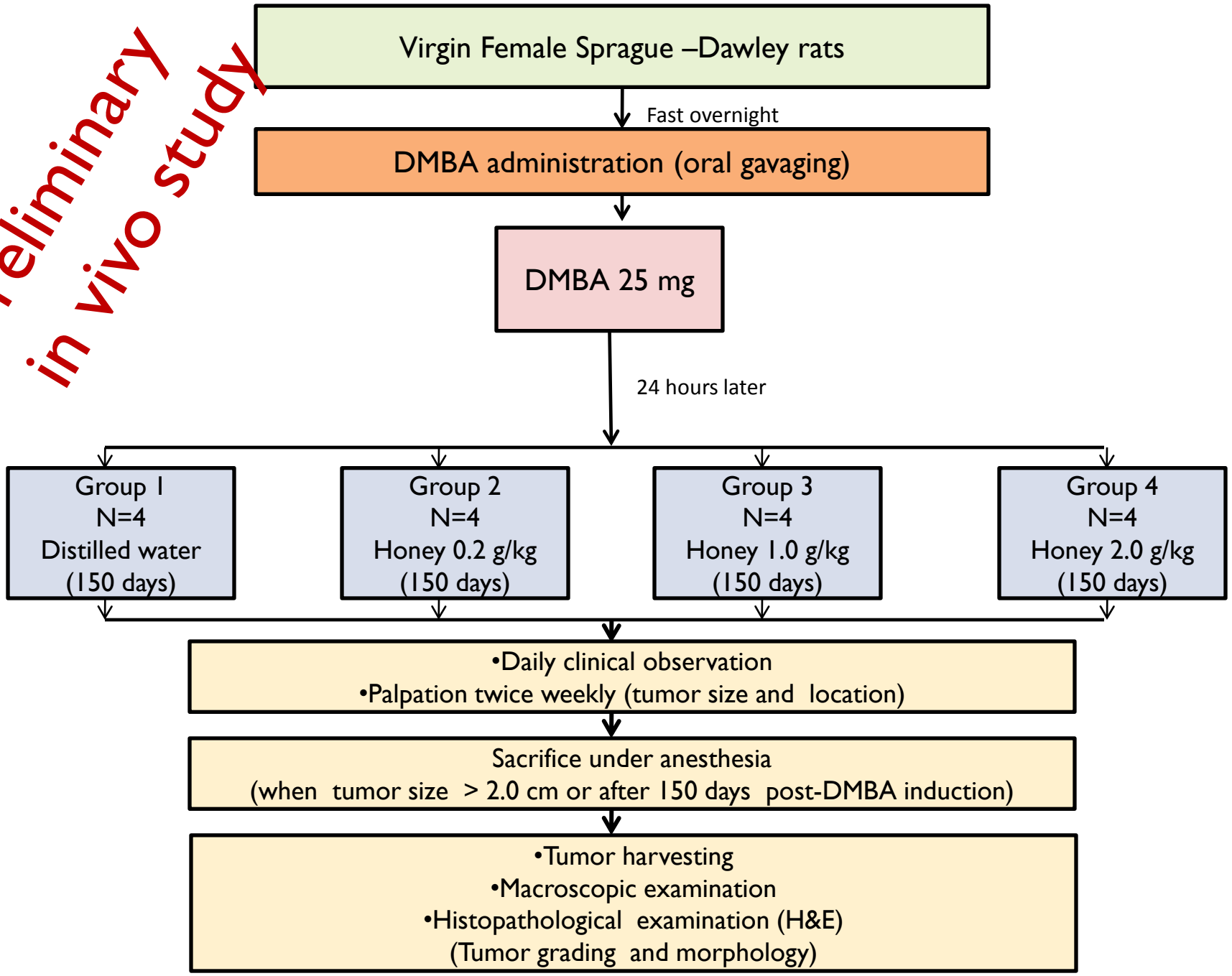


Tualang honey induced apoptotic cell death in OSCC and HOS cell lines.

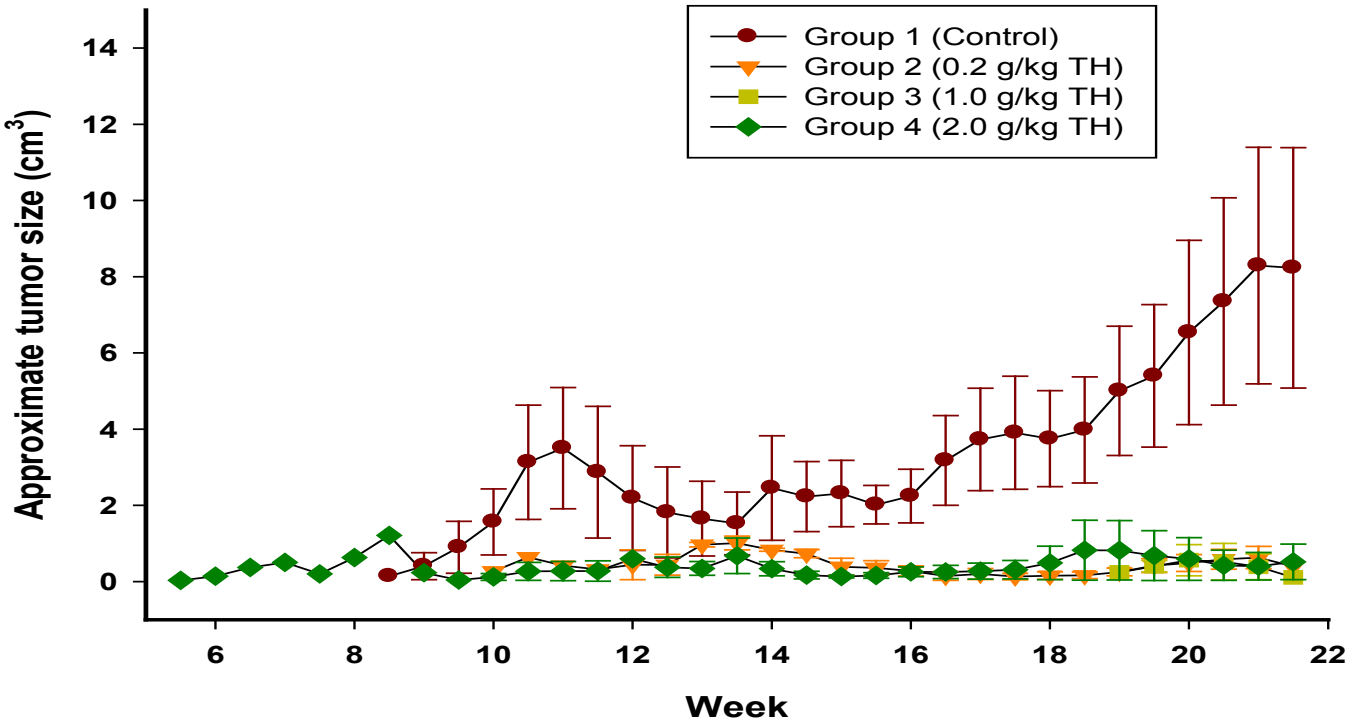
Effect of Tualang honey on morphology of (a) OSCC and (b) HOS cell lines as seen under light microscope. Cells were cultured in 6-well plates until 70-80% confluence and then treated with Tualang honey 2% and 10% for 24, 48 and 72 hrs

BMC Complementary and Alternative Medicine 2010, 10:49,pp2-8._doi:10.1186/1472-6882-10-4.

Preliminary in vivo study



Tumor progression

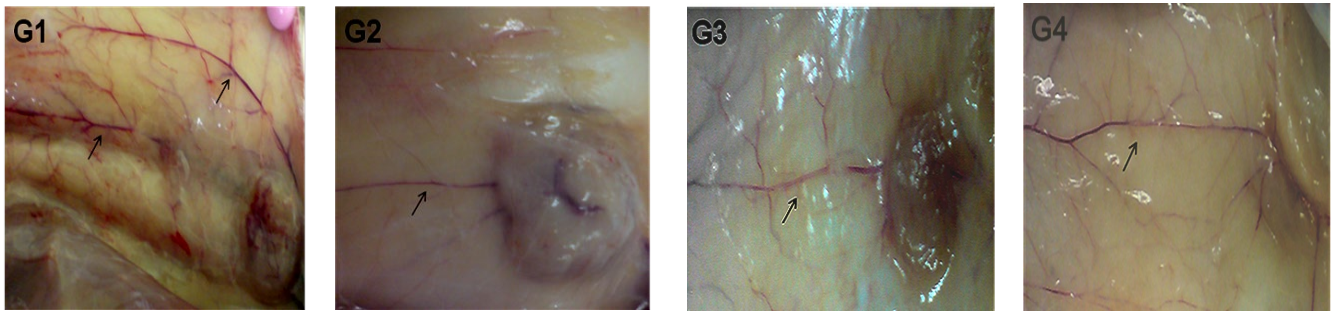


- Non- Honey : Rapid tumor size increment over shorter period of time
- Honey : Slower tumor size increment & lesser mean tumor size

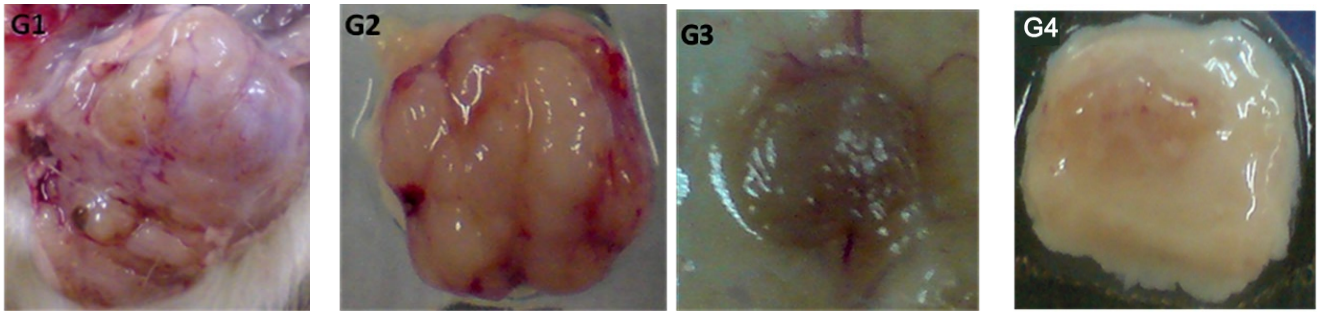
Study groups

G1	G2	G3	G4
Control	0.2 g/kg/day TH	1.0 g/kg/day TH	2.0 g/kg/day TH

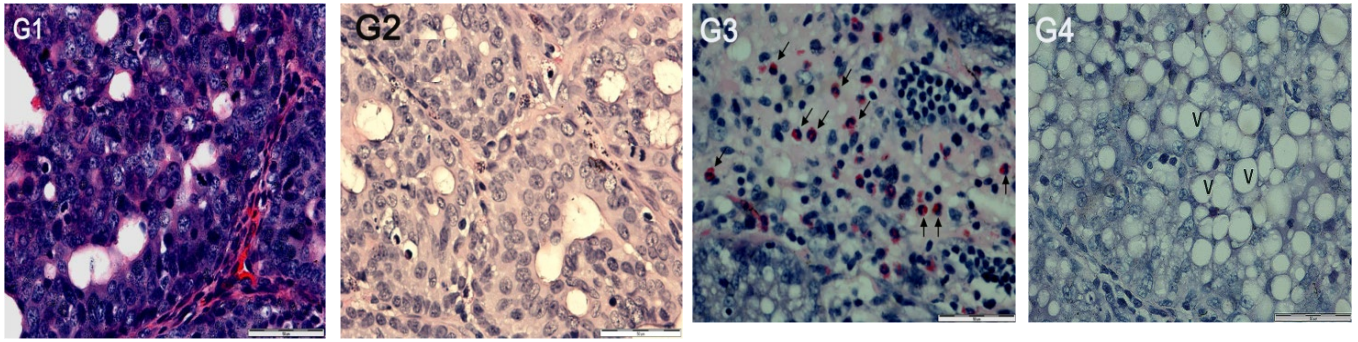
The vasculature around the cancer masses. Arrows showing the arteries supplying the cancer mass

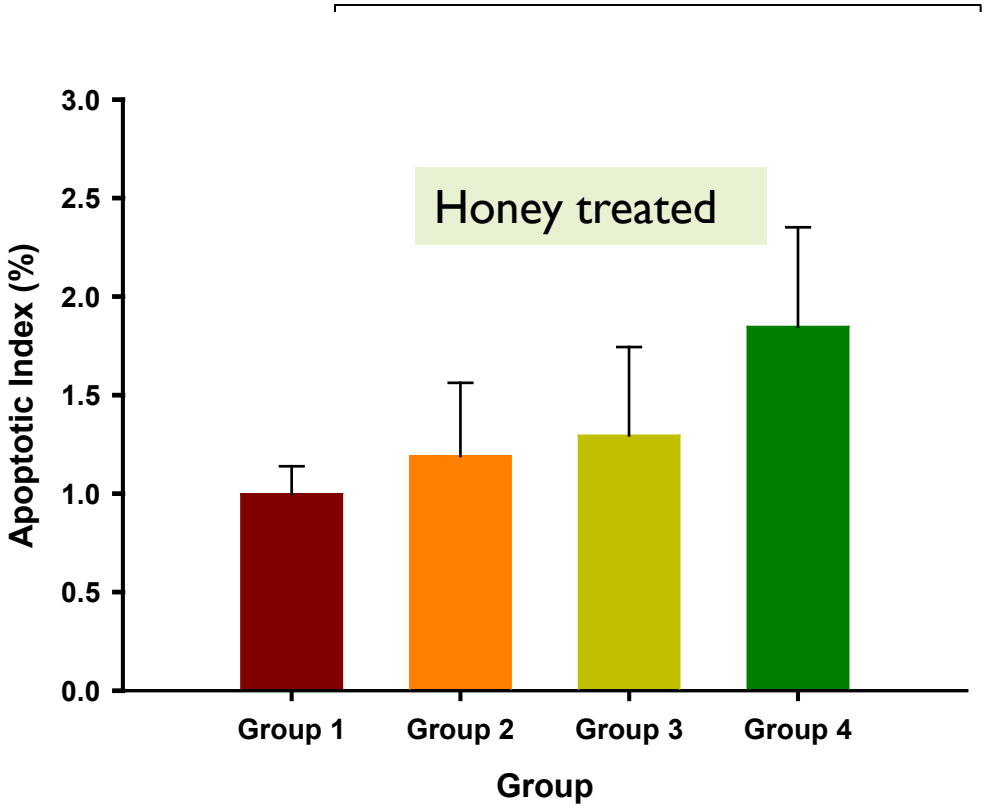


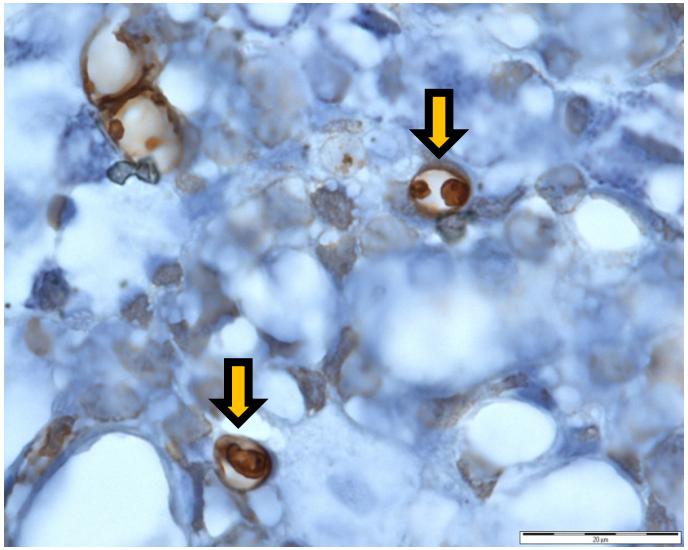
The gross appearance of the cancer after 150 days post-DMBA induction.



The histology of the breast cancer. The H/E stained sections examined under light microscope at X400 magnification [Arrows in G3 showing eosinophils; 'V' in G4 showing vacuoles in cancer cells

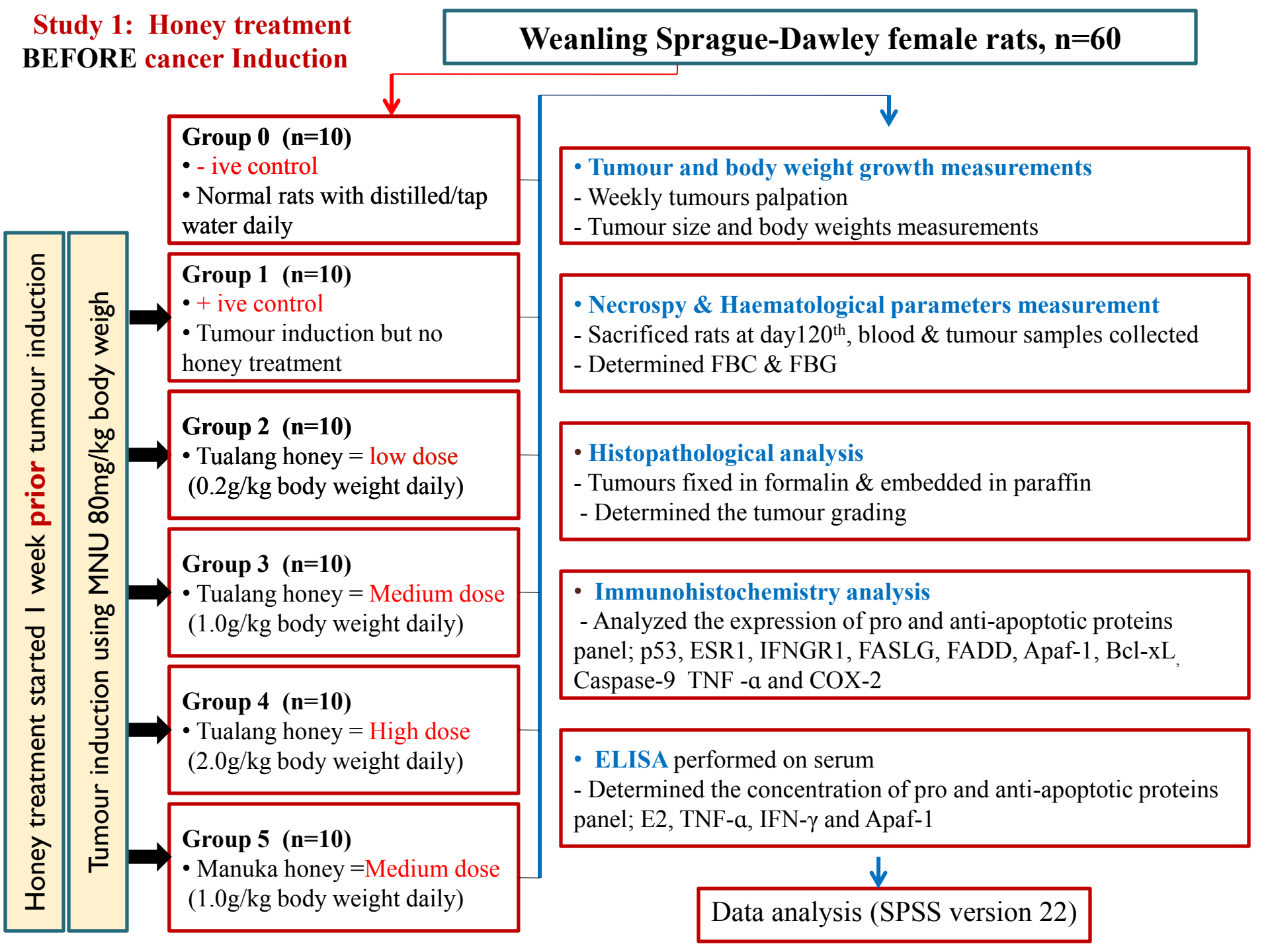


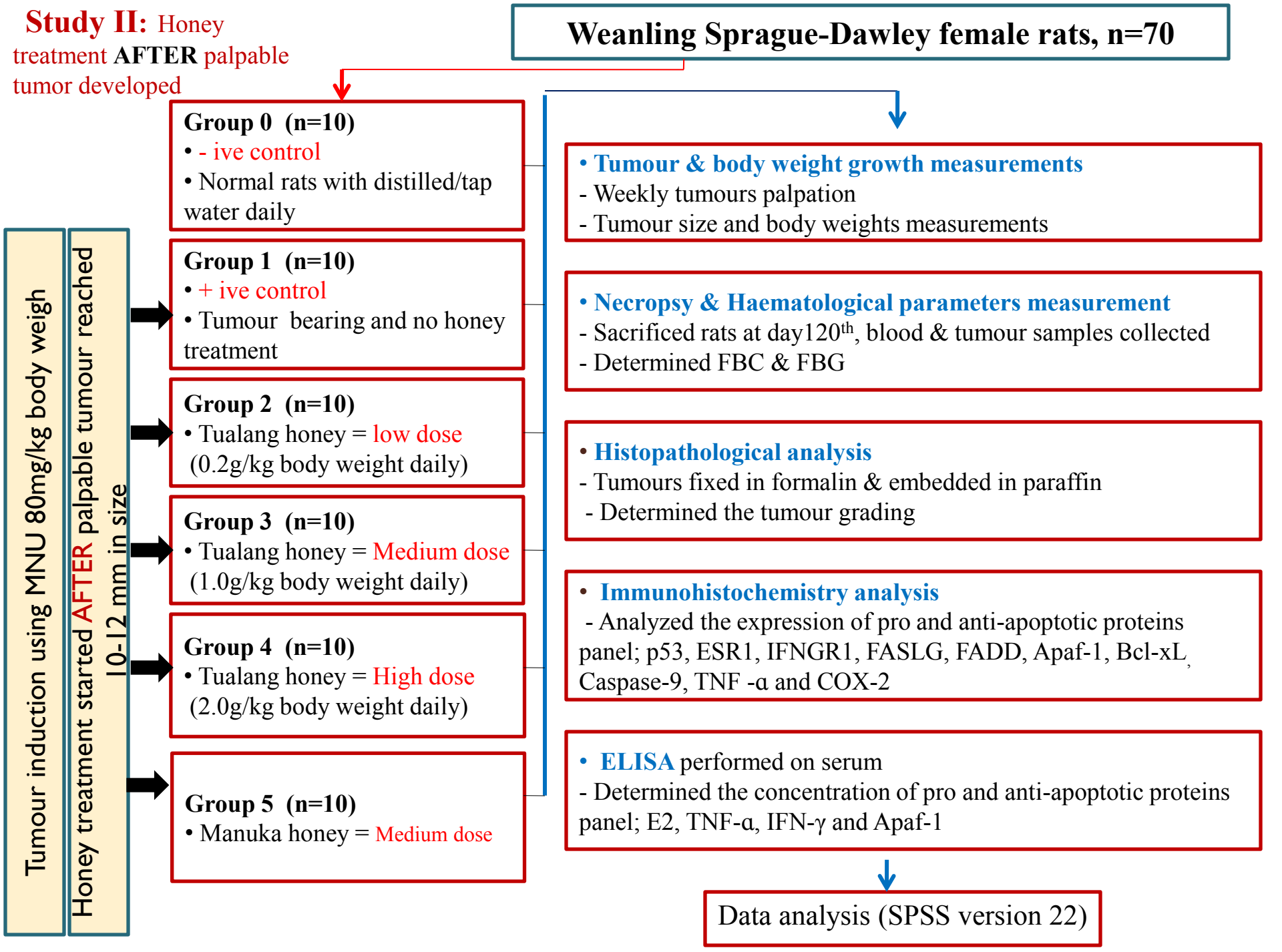




- Bar graph: Percentage of apoptotic cells per total number of cells counted (AI).
- Photomicrograph: Brown-colored apoptotic cells from TUNEL assay (1000x).
- Increasing trend of AI with increasing dose of honey treatment .
- Differences between groups – statistically not significant.

BMC Complementary and Alternative Medicine 2010, 10:49,pp2-8._doi:10.1186/1472-6882-10-4.


Study 1: Honey treatment BEFORE cancer Induction
Weanling Sprague-Dawley female rats, n=60
Honey treatment started 1 week prior tumour induction
Tumour induction using MNU 80mg/kg body weigh
Group 0 (n=10)
• - ive control
• Normal rats with distilled/tap water daily
Group 1 (n=10)
• + ive control
• Tumour induction but no honey treatment
Group 2 (n=10)
• Tualang honey = low dose (0.2g/kg body weight daily)
Group 3 (n=10)
• Tualang honey = Medium dose (1.0g/kg body weight daily)
Group 4 (n=10)
• Tualang honey = High dose (2.0g/kg body weight daily)
Group 5 (n=10)
• Manuka honey =Medium dose (1.0g/kg body weight daily)
• Tumour and body weight growth measurements
- Weekly tumours palpation
- Tumour size and body weights measurements
• Necrospy & Haematological parameters measurement
- Sacrificed rats at day120th, blood & tumour samples collected
- Determined FBC & FBG
• Histopathological analysis
- Tumours fixed in formalin & embedded in paraffin
- Determined the tumour grading
• Immunohistochemistry analysis
- Analyzed the expression of pro and anti-apoptotic proteins panel; p53, ESR1, IFNGR1, FASLG, FADD, Apaf-1, Bcl-xL, Caspase-9 TNF -α and COX-2
• ELISA performed on serum
- Determined the concentration of pro and anti-apoptotic proteins panel; E2, TNF-α, IFN-γ and Apaf-1
Data analysis (SPSS version 22)


Study II: Honey treatment AFTER palpable tumor developed
Weanling Sprague-Dawley female rats, n=70
Tumour induction using MNU 80mg/kg body weigh
Honey treatment started AFTER palpable tumour reached 10-12 mm in size
Group 0 (n=10)
• - ive control
• Normal rats with distilled/tap water daily
Group 1 (n=10)
• + ive control
• Tumour bearing and no honey treatment
Group 2 (n=10)
• Tualang honey = low dose (0.2g/kg body weight daily)
Group 3 (n=10)
• Tualang honey = Medium dose (1.0g/kg body weight daily)
Group 4 (n=10)
• Tualang honey = High dose (2.0g/kg body weight daily)
Group 5 (n=10)
• Manuka honey = Medium dose
• Tumour & body weight growth measurements
- Weekly tumours palpation
- Tumour size and body weights measurements
• Necropsy & Haematological parameters measurement
- Sacrificed rats at day120th, blood & tumour samples collected
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• Immunohistochemistry analysis
- Analyzed the expression of pro and anti-apoptotic proteins panel; p53, ESR1, IFNGR1, FASLG, FADD, Apaf-1, Bcl-xL, Caspase-9, TNF -α and COX-2
• ELISA performed on serum
- Determined the concentration of pro and anti-apoptotic proteins panel; E2, TNF-α, IFN-γ and Apaf-1
Data analysis (SPSS version 22)

Tumour Induction

a) MNU dissolved in 0.9% NaCl solution

b) Acidified to pH=5.0 with 0.05% acetic acid

(Thompson and Adlakha, 1991)

I.P injection to Sprague-Dawley rats,

80mg/kg body weight

at age 40 days old

Animals Experimentation

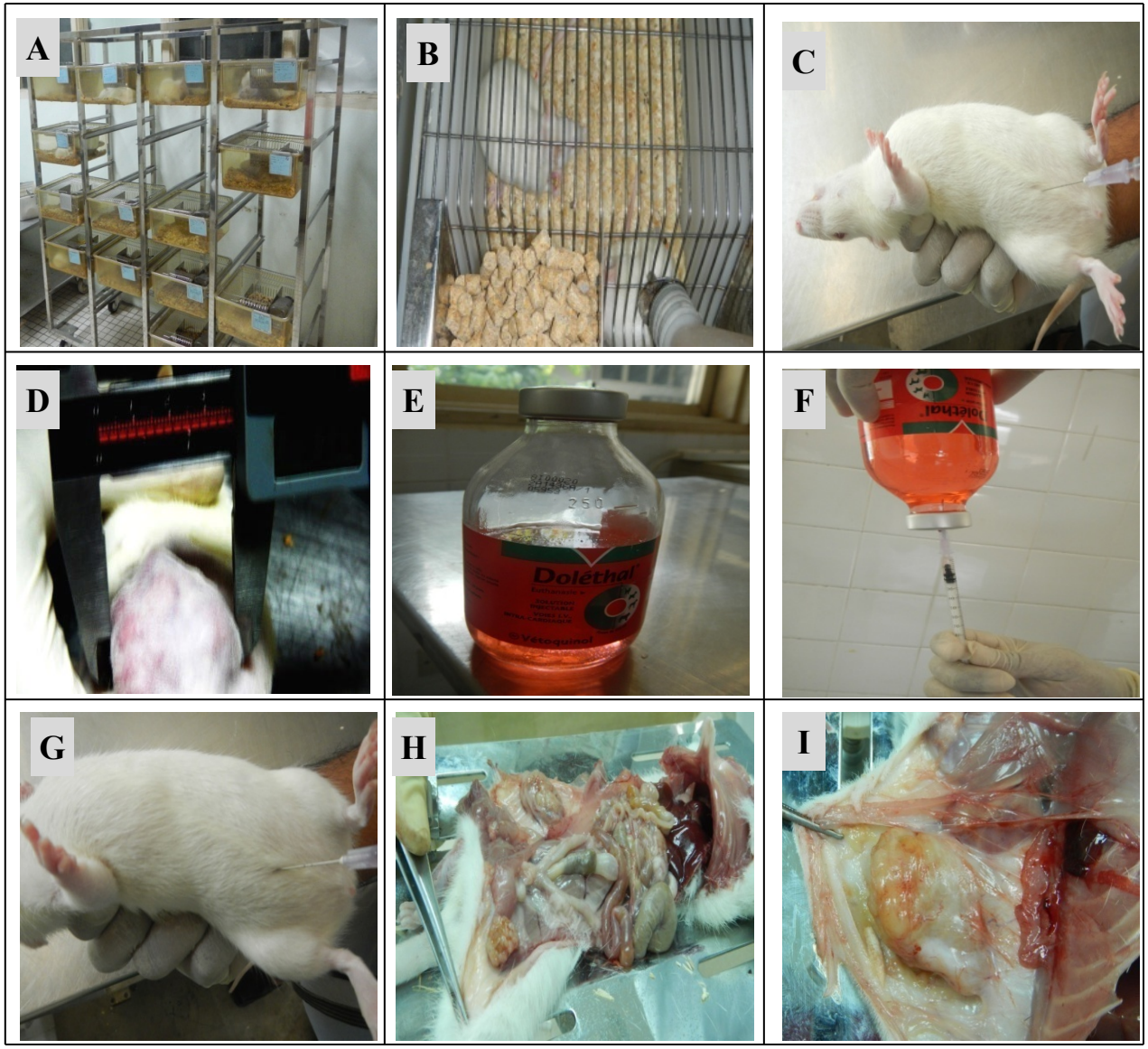
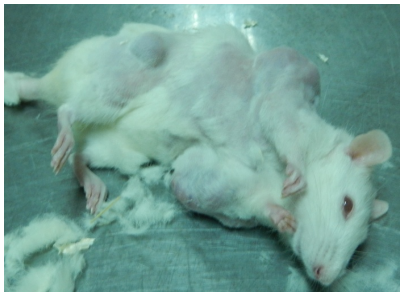
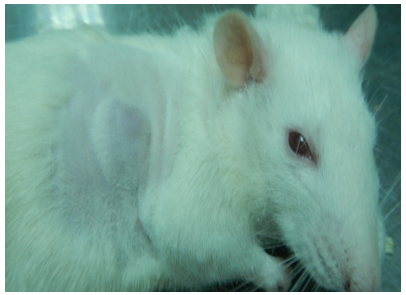
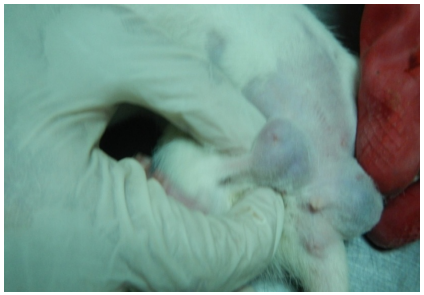
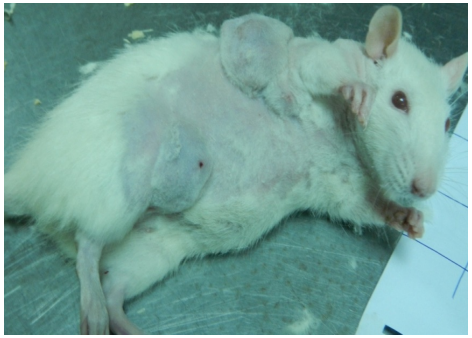
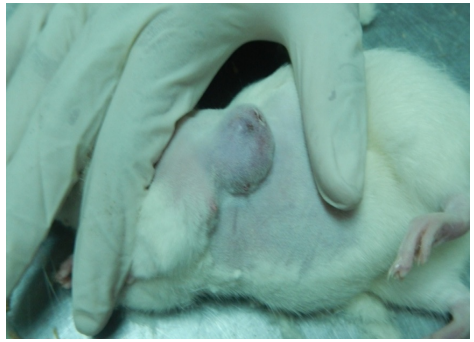


Figure: Animals experimentation: A & B; The rats maintenance C; intraperitoneal (i.p) injection of carcinogen MNU, D; tumour measurements, E, F & G; Sedation , H & I; Necropsy for samples collection.

RESULTS

Cancer- preventive Study

(Honey treatment started a week before MNU-induction)

Cancer- therapeutic Study

(Honey treatment started after breast cancer is palpable)

The Physical Characteristics of Tumour Growth [Preventive study (honey treatment 7/7 BEFORE cancer induction)

Tumours	Groups						P value
	0 - ive control	1 +ive control	2 (0.2g/kg TH)	3 (1.0g/kg TH)	4 (2.0g/kg TH)	5 (1.0g/kg MH)	
* Incidence (%)	No tumour	100	80	80	70	60	0.406
** Latency (days)	No tumour	51.5 (14.75)	75.5 (29.75)	76.5 (19.25)	74 (23)	74.5 (14.5)	0.015
** Multiplicity	No tumour	4 (2.25)	2.5 (2.75)	3 (2.5)	2 (2)	2 (3)	0.190
** Size (cm^3)	No tumour	1.47 (2.78)	0.26 (0.86)	0.38 (1.48)	0.60 (1.297)	0.23 (0.56)	0.000
** Weight (g)	No tumour	3.23 (7.23)	1.23 (5.23)	1.17 (2.50)	1.27 (2.97)	0.92 (2.67)	0.005

*Fisher Exact test. Values are statistically significant when $p \leq 0.05$.
**Kruskal-Wallis test. Data are expressed as median interquartile range (IqR). Values are statistically significant when $p \leq 0.05$.

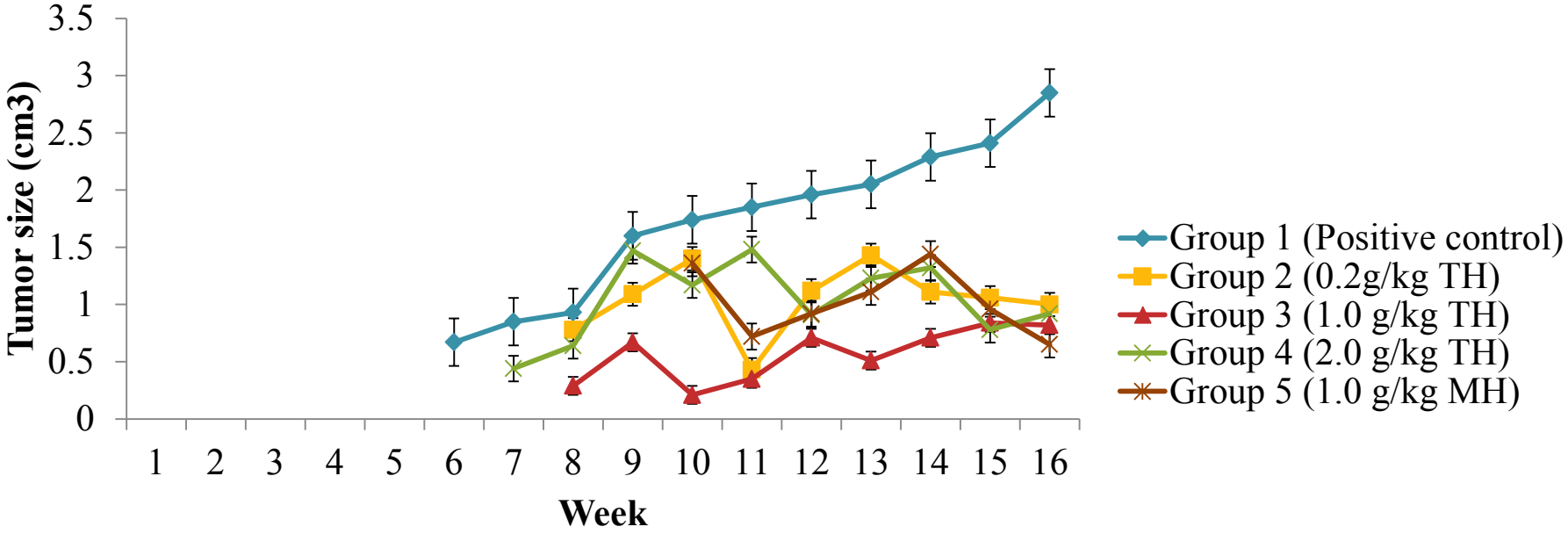
***TH and MH potentiate the latency and lower the tumour incidence, multiplicity, size and weight**

The Physical Characteristics of Tumour Growth [Therapeutic study (honey treatment AFTER cancer is palpable)

	Groups						
Tumours	**1 +ive control**	**2 (0.2g/kg TH)**	**3 (1.0g/kg TH)**	**4 (2.0g/kgTH)**	**5 (1.0g/kg MH)**	**6 (1.0g/kg HSA)**	**P value[a]**
Multiplicity	**5 (4)**	**3.5 (2.25)**	**3 (5.25)**	**3.5 (1.5)**	**3 (3.5)**	**3 (3.5)**	**0.462**
***% Reduction**	**0 (0)**	**54.8(43)**	**70.82(22.94)**	**33.97(60.4)**	**57 (32.94)**	**58.53(37.97)**	**0.000**
***Size (cm^3)**	**1.23 (2.49)**	**0.19 (1.6)**	**0.17 (0.29)**	**0.50 (1.94)**	**0.44 (1.11)**	**0.23 (0.54)**	**0.000**
***Weight (g)**	**2.55 (7.76)**	**0.68 (5.37)**	**0.89 (2.62)**	**1.65 (5.85)**	**1.8 (3.70)**	**1.25 (2.53)**	**0.011**

- **TH, MH and HSA showed a potentiating effect on % reduction**
- **TH, MH and HSA had a lowering effect on Tumour Multiplicity, Size and Weigh**

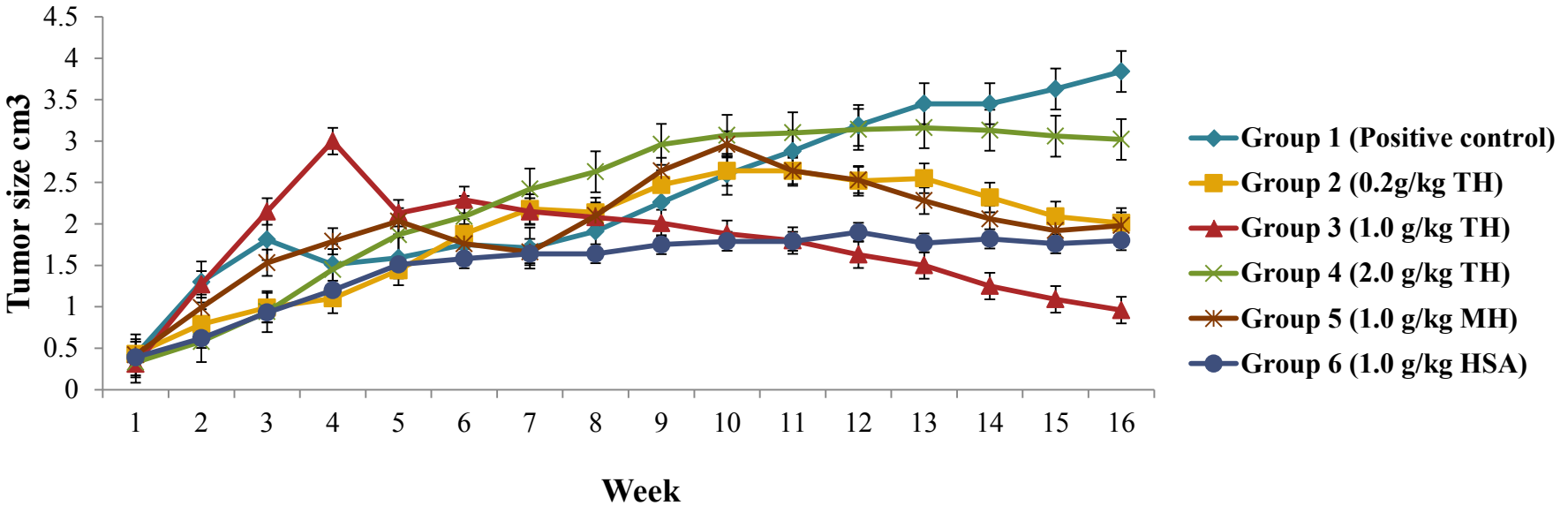
Breast Cancer Progression
(honey treatment 7/7 BEFORE cancer induction)



- All strengths of TH and MH appeared to slow down the progression of breast tumour development during the experimental period.

- In contrast, the non-treated control rats exhibited increased tumour progression with faster tumour size increment.

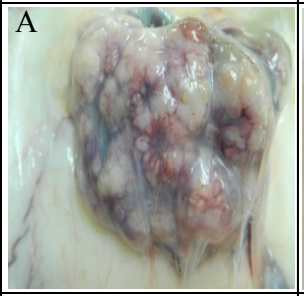
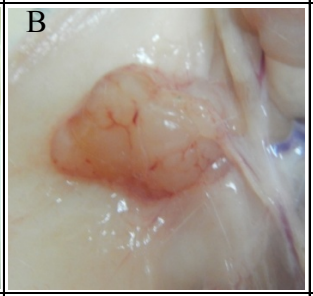
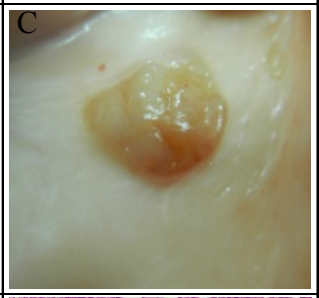
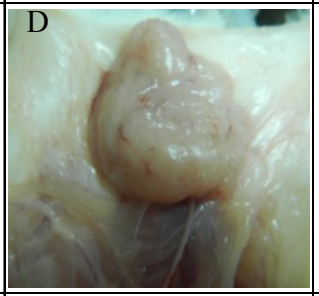
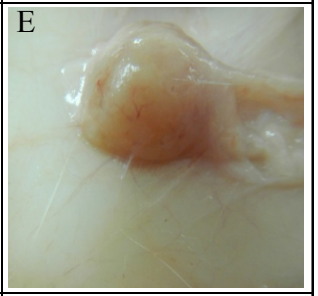
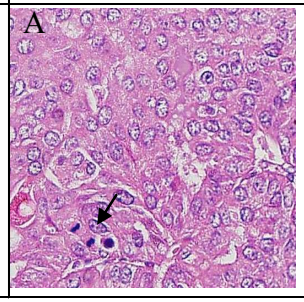
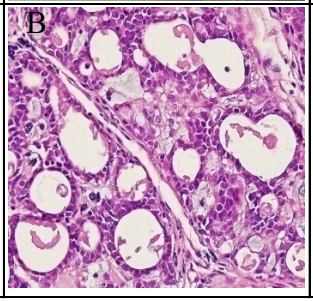
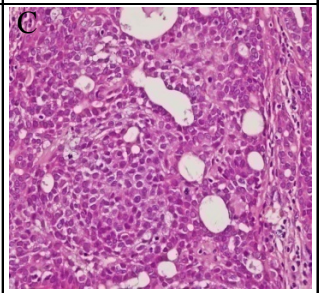
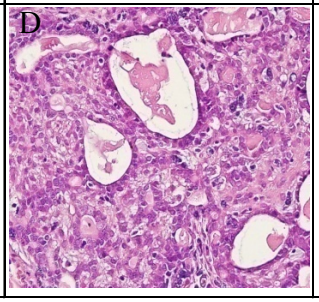
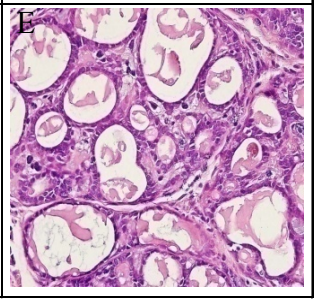
Breast Cancer Progression
(honey treatment started AFTER cancer is palpable)



- All strengths of TH, MH and HSA appeared to slow down the progression of breast tumour development during the experimental period.

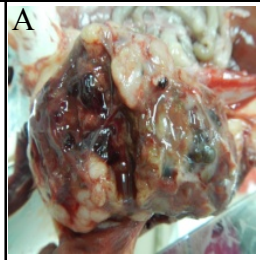
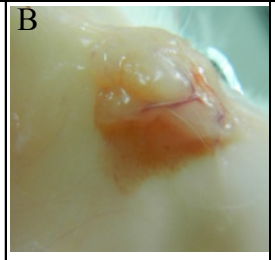
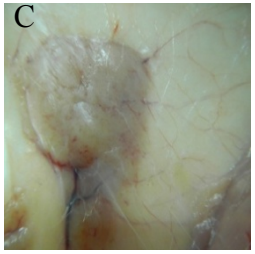
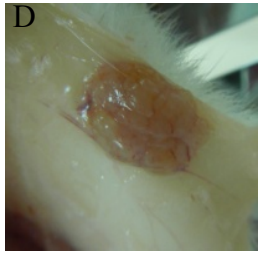
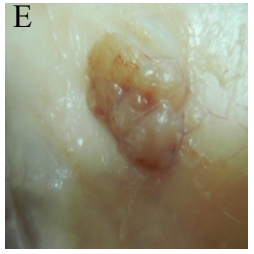
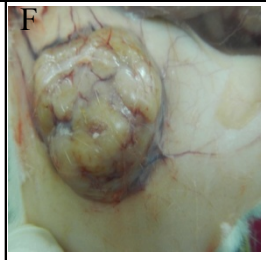
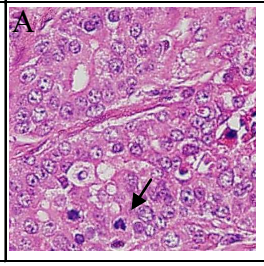
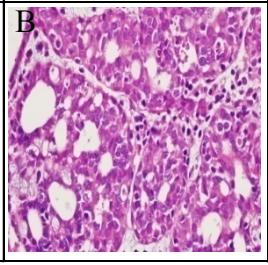
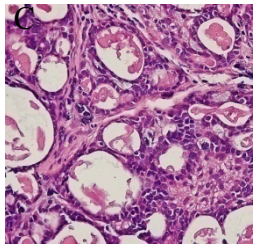
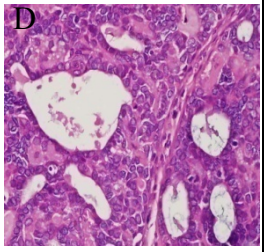
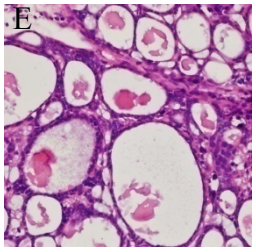
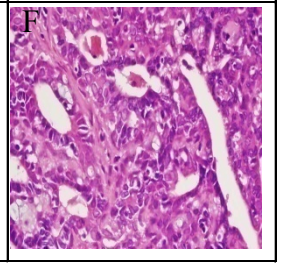
- In contrast, the non-treated control rats exhibited increased tumour progression with faster tumour size increment.

Gross Morphology & Histopathology of Breast Cancer (honey treatment 7/7 BEFORE cancer induction)

Study groups	Group 1 +ive control (no treatment)	Group 2 0.2 g/kg TH	Group 3 1.0 g/kg TH	Group 4 2.0 g/kg TH	Group 5 1.0 g/kg MH
The gross appearance of tumours					
The H & E histology at X400 (Arrow shows mitosis)					

The tumour masses in the non-treated control larger in size, solid, hard in consistency and of higher grade compared to treated groups with softer, paler, smaller in size and of lower grade.

Gross Morphology & Histopathology of Breast Cancer (honey treatment started AFTER cancer is palpable)

Study groups	Group 1 +ive control (no treatment)	Group 2 0.2 g/kg TH	Group 3 1.0 g/kg TH	Group 4 2.0 g/kg TH	Group 5 1.0 g/kg MH	Group 6 1.0 g/kg HSA
The gross appearance						
Figure 4.b The H & E histology at X400 (arrow shows mitosis)						

The tumour masses in the non-treated control larger in size, solid, hard in consistency and of higher grade compared to treated groups with softer, paler, smaller in size and of lower grade.

Histological Grading* of Breast Cancer (honey treatment 7/7 BEFORE cancer induction)

	Groups					
Tumours	**0 - ive control**	**1 +ive control**	**2 (0.2g/kg TH)**	**3 (1.0g/kg TH)**	**4 (2.0g/kg TH)**	**5 (1.0g/kg MH)**
Total No.	**No tumour**	**39**	**18**	**22**	**17**	**11**
***Grade I (%)**	**No tumour**	**7 (17.94)**	**11 (61.11)**	**9 (40.90)**	**9 (52.94)**	**8 (72.72)**
***Grade II (%)**	**No tumour**	**10 (25.64)**	**2 (11.11)**	**9 (40.90)**	**6 (35.29)**	**3 (27.27)**
***Grade III (%)**	**No tumour**	**22 (56.41)**	**5 (27.77)**	**4 (18.18)**	**2 (11.76)**	**0**

TH and MH exhibit tumours mainly of grade I and II (histologically less aggressive) compared to the non-treated control which had majority of grade III (histologically more aggressive).

* Bloom-Richardson Grading system

Histological Grading of Breast Cancer
(honey treatment AFTER cancer is palpable)

		Groups					
Tumours	**0** **- ive control**	**1** **+ive control**	**2** **(0.2g/kg TH)**	**3** **(1.0g/kg TH)**	**4** **(2.0g/kg TH)**	**5** **(1.0g/kgMH)**	**6** **(1.0g/kgHSA)**
Total No.	**No tumour**	**47**	**27**	**23**	**32**	**33**	**26**
***Grade I (%)**	**No tumour**	**6 (12.76)**	**8 (29.62)**	**14 (60.86)**	**8 (25)**	**22 (66.66)**	**11 (42.3)**
***Grade II (%)**	**No tumour**	**15 (31.91)**	**14 (51.85)**	**5 (21.73)**	**21 (65.62)**	**9 (27.27)**	**11 (42.3)**
***Grade III(%)**	**No tumour**	**26 (55.31)**	**5 (18.51)**	**4 (17.39)**	**3 (9.37)**	**2 (6.06)**	**4 (15.38)**

*Fisher Exact test, statistically a significant difference between the groups, $p < 0.05$.

*TH, MH and HSA exhibit tumours mainly of grade I and II (histologically less aggressive) compared to the non-treated control which had majority of grade III (histologically more aggressive).

Hematological Parameters
(honey treatment 7/7 BEFORE cancer induction)

Blood parameter	Groups						
	0 - ive control	1 +ive control	2 (0.2g/kg TH)	3 (1.0g/kg TH)	4 (2.0g/kg TH)	5 (1.0g/kg MH)	P value[a]
RBC (10^{12}/L)	7.15 (0.27)	6.35 (0.75)	7.35 (1.22)	7.4 (1.02)	6.85 (1.67)	7.15 (0.82)	0.088
Hb (g/dl)	15.35 (0.62)	14.1 (1.62)	14.8 (1.92)	15 (1.97)	15.25 (2.77)	14.9 (1.37)	0.062
*PCV (%)	48 (2.5)	42 (3.25)	48.5 (5)	48.5 (9)	47.5 (8.75)	48.5 (5)	0.047
MCV (fl)	65.5 (1.5)	66 (4.75)	65.5 (6.75)	66 (1.75)	65.5 (3.75)	65.5 (5.25)	0.004
MCH (pg)	21 (2)	21.5 (1.5)	20.5 (2.25)	21 (2.25)	21.5 (2)	21 (2)	0.958
MCHC (g/L)	32.5 (1)	31.5 (1.75)	31 (1.5)	31 (2.5)	32 (3)	32.5 (1)	0
*RDW (%)	11.85 (1.7)	13.85 (1.7)	12.25 (2.72)	12.6 (1.5)	12.9 (2.22)	12.65 (1.5)	0.01
TWBC (10^9/L)	4.85 (1.75)	6.14 (8.72)	5.05 (2.4)	4.95 (6)	6.25 (5.7)	4.85 (2.67)	0.178
*Polymorphs (%)	33 (9.5)	42 (19.75)	34 (16.5)	32 (12)	32.5 (13.5)	32.5 (6.5)	0.009
*Lymphocytes(%)	66 (5.5)	54 (20.75)	65 (13.5)	64.5 (13.5)	66.5 (15)	67 (5.75)	0.01
Monocytes (%)	1.5 (1.5)	1.5 (2.5)	1.25 (1)	1 (0)	1 (2)	1 (2.25)	0.649
Eosinophils (%)	0 (1.25)	0 (1.25)	0	0 (2)	0.5 (1)	0 (1)	0.534
Basophils (%)	0		0	0	0	0	1
*Platelets' (10^9/L)	809.5 (149)	627.5 (196.75)	734 (197)	758.5 (178)	710 (89.5)	681 (236)	0.042
Glucose (mg/dl)	164 (61.75)	126.5 (59.75)	106.5 (92)	132 (72.5)	123 (59.5)	123.5 (72.5)	0.899

[a]Kruskal-Wallis test. Data are expressed as median interquartile range (IqR). Values are statistically significant at $p \leq 0.05$.

1. Treatments with TH and MH had a slight potentiating effect on level of RBC, Hb, PCV, lymphocytes, platelets and eosinophils

2. A slight lowering effect on RDW, TWBC, polymorphs, monocytes and FBG compared to the non-treated positive control.

Hematological Parameters
(honey treatment started AFTER cancer is palpable)

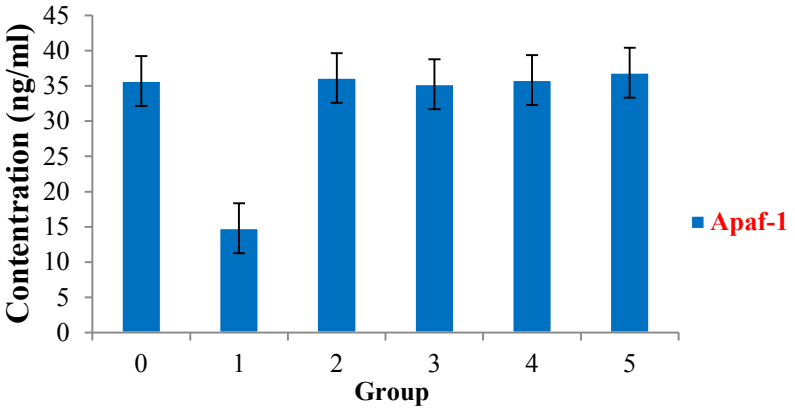
Blood parameter	Groups						
	0 - ive control	1 +ive control	2 (0.2g/kg TH)	3 (1.0g/kg TH)	4 (2.0g/kg TH)	5 (1.0g/kg MH)	6 (1.0g/kgHSA)
*RBC (10^{12}/L)	7.35 (0.42)	5.1 (0.9)	6.3 (2.27)	6.8 (3.32)	6.25 (1.62)	6.15 (2.75)	6.85 (1.1)
*Hb (g/dl)	15.2 (0.77)	11.35 (1.42)	14.4 (4.17)	13.85 (5.95)	13.25 (2.9)	13.85 (4.45)	15.1 (1.45)
*PCV (%)	46 (3.25)	35 (8.25)	39.5 (9.5)	42.5 (17.75)	43 (14.5)	43.5 (12.25)	45 (7.5)
*MCV (fl)	68.5 (3.25)	65 (4.75)	66.5 (12.75)	65 (11.75)	65 (5.25)	67 (10.25)	65 (4.5)
MCH (pg)	20.5 (1)	21 (2)	21.5 (1.75)	21 (3)	20.5 (1)	21 (3.5)	21 (1.5)
MCHC (g/L)	32 (1)	31.5 (2.25)	32 (5.25)	32 (3.5)	31.5 (3.25)	31.5 (2.25)	32 (5)
*RDW (%)	11.9 (1.57)	13.95 (1.72)	14.4 (2.5)	12.25 (2.17)	14.1(1.82)	12.65 (2.1)	12.2 (1.8)
*TWBC (10^9/L)	4.75 (1.75)	6.4 (7.52)	12 (19.7)	4.82 (8.75)	10.3 (4.17)	7.35 (6.85)	5.6 (3.15)
*Polymorphs(%)	32 (8.75)	46.5 (18)	32.5 (12)	31.5 (11.25)	31 (10.25)	31.5 (9.5)	32 (16)
*Lymphocytes(%)	68 (8)[i]	49 (19.25)	68 (9.25)	69 (9.75)	67 (9.25)	67.5 (4.5)	68 (14.5)
Monocytes (%)	2 (1.5)	2.5 (3.5)	1 (1.25)	0.5 (1)	1 (3.25)	1 (4.25)	1 (2.5)
Eosinophils (%)	0 (1)	0 (1.25)	0.5 (11)	0.5 (1)	1 (1.25)	1 (0.25)	1 (1)
Basophils (%)	0	0	0	0	0	0	0
Platelets (10^9/L)	839 (225.75)	627.5 (196.75)	640 (389.75)	666.5 (229.25)	548.5 (337.5)	540.5 (324.75)	768 (255)
Glucose (mg/dl)	164 (53)	127.5 (58.5)	138.05 (51)	153.5 (66.25)	154 (123.75)	138 (50.5)	142 (71.5)

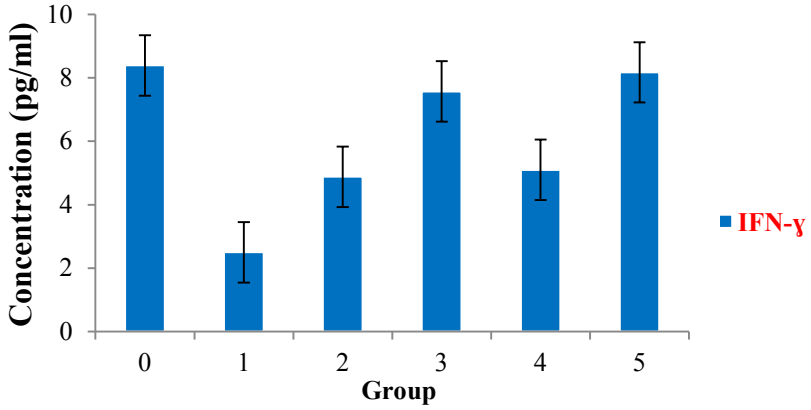
[a]Kruskal-Wallis test. Data are expressed as median interquartile range (IqR).* Values are statistically significant when $p \leq 0.05$.

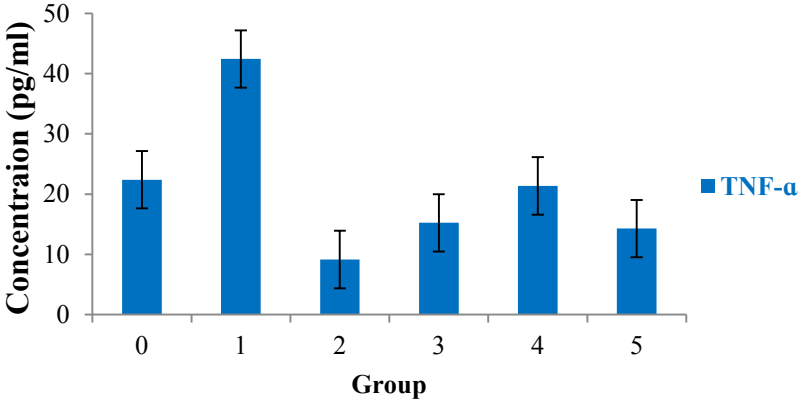
Treatments with TH, MH and HSA had a slight potentiating effect on level of RBC, Hb, PCV, MCV lymphocytes, platelets, eosinophils and FBG (not exceeding than normal)

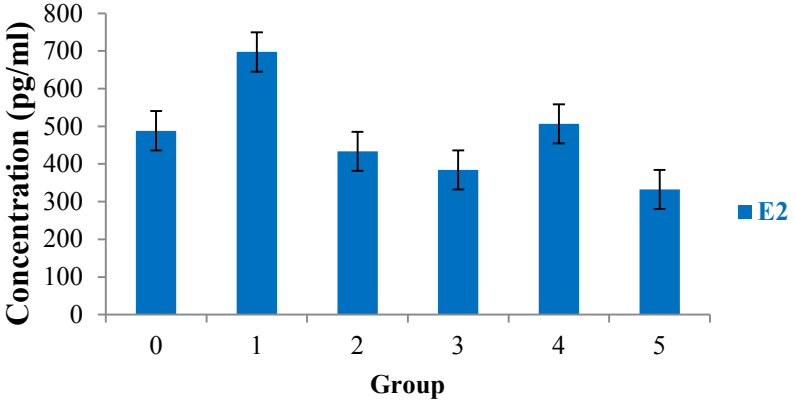
A slight lowering effect on RDW, TWBC, polymorphs and monocytes compared to non-treated positive control.

Serum Level Concentration of Pro and Anti-apoptotic Proteins (honey treatment 7/7 BEFORE cancer induction)



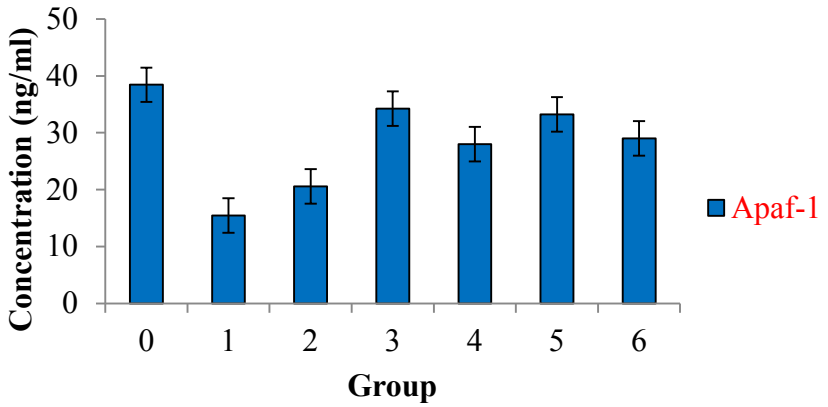


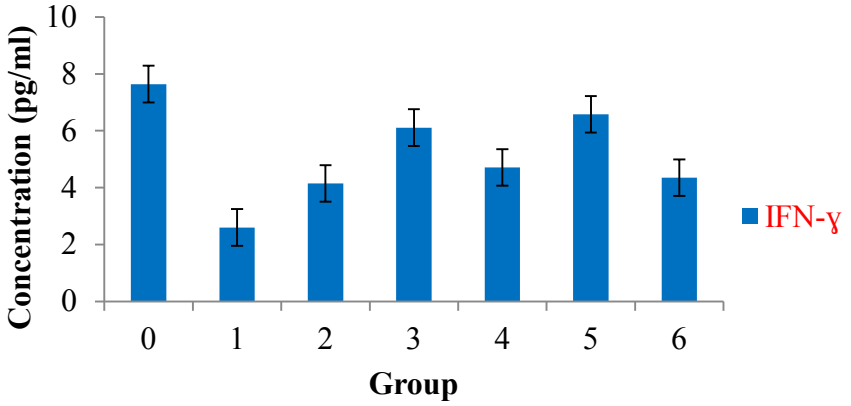


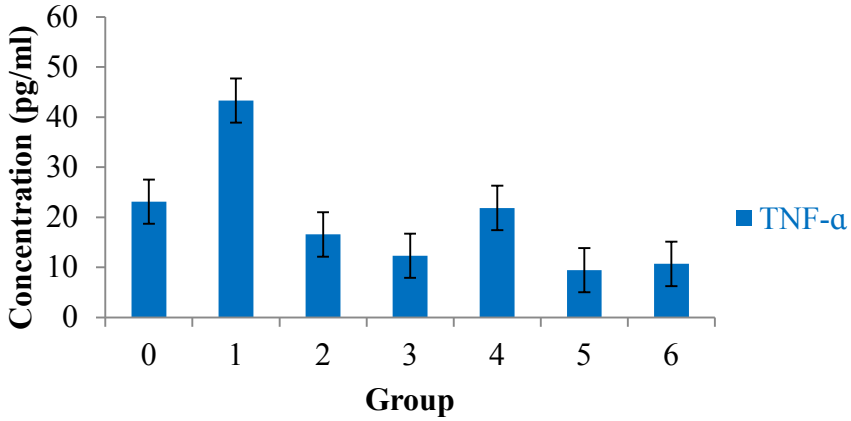


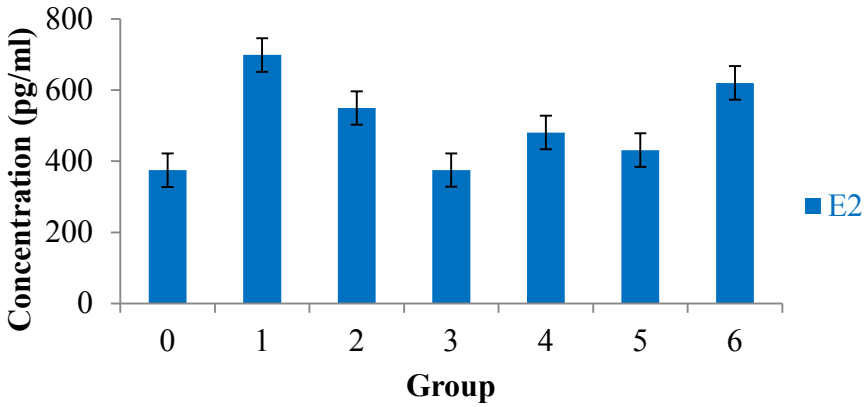
- **TH and MH showed a potentiating effect on level of pro-apoptotic proteins; Apaf-1 and IFN-ɣ**
- **A lowering effect on level of anti-apoptotic proteins; TNF-α and E2 compared to non-treated positive control**

Serum Level Concentration of Pro and Anti-apoptotic Proteins (honey treatment started AFTER cancer is palpable)









- TH, MH and HSA showed a potentiating effect on level of pro-apoptotic proteins; Apaf-1 and IFN-ɣ

- A lowering effect on level of anti-apoptotic proteins; TNF-α and E2 compared to non-treated positive control

Immunohistochmical Expression (%)of Pro and Anti-apoptotic Proteins at Cancer Tissues level
(honey treatment 7/7 BEFORE cancer induction)

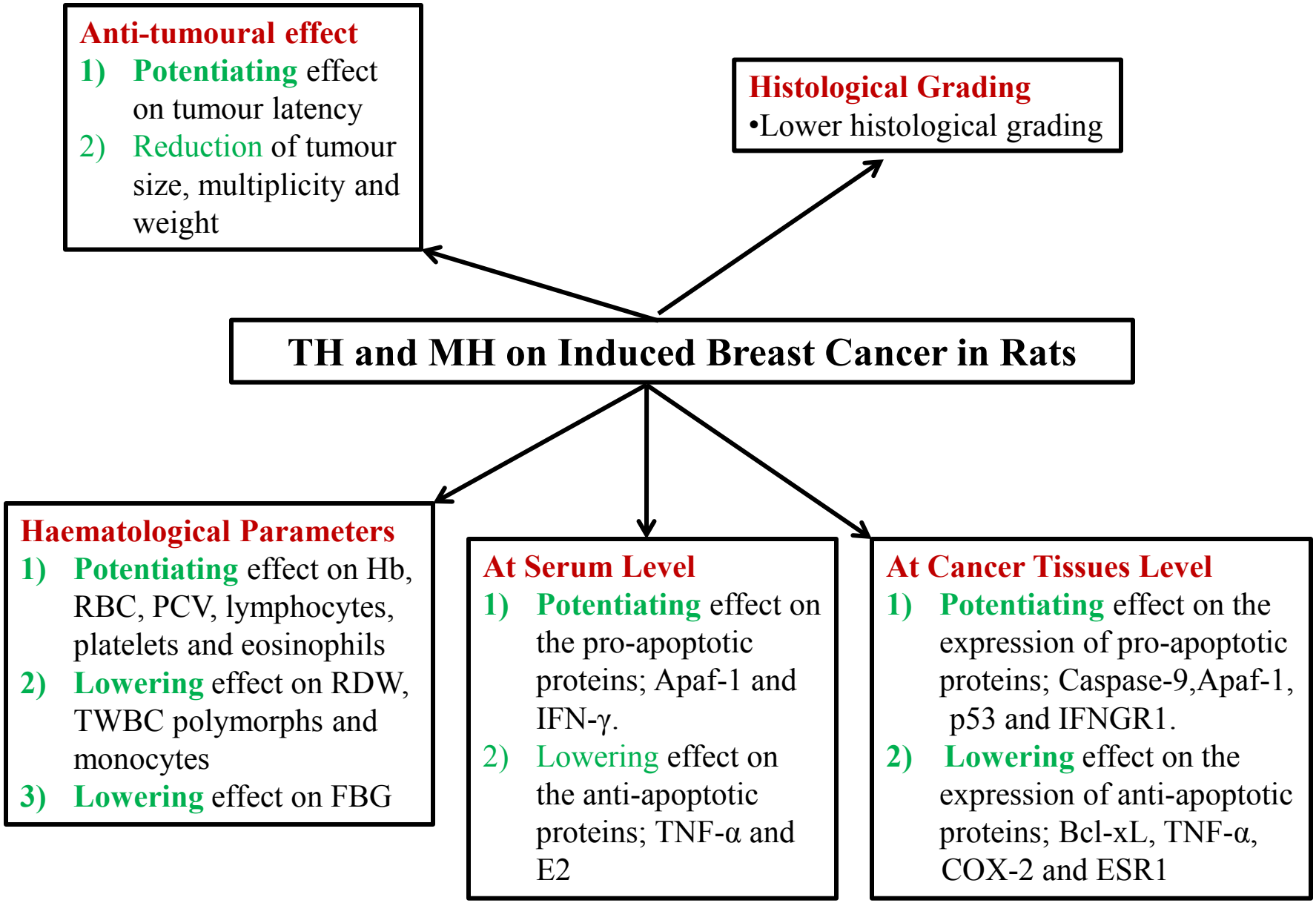
Tumours	No. of positive tumours (% expression or positivity)									
Group	**No of tm**	**Caspase-9**	**Apaf-1**	**P53**	**IFNGR1**	**FASLG**	**FADD**	**Bcl-xL**	**TNF-α**	**COX-2**	**ESR1**
1 +ive control	**35**	**16 (45.7)**	**15(42.9)**	**17(48.6)**	**20(57.1)**	**13(37.1)**	**12(34.3)**	**28 (80)**	**31(88.6)**	**23(65.7)**	**26 (74.3)**
2 (0.2g/kg TH)	**16**	**13 (81.3)**	**15 (93.8)**	**13 (85)**	**15(93.8)**	**-ive**	**-ive**	**9 (56.3)**	**13 (85)**	**7 (43.8)**	**8 (50)**
3 (1.0g/kg TH)	**20**	**14 (70)**	**16 (80)**	**13 (65)**	**15 (75)**	**-ive**	**-ive**	**10 (50)**	**11 (55)**	**9 (45)**	**11 (55)**
4 (2.0g/kg TH)	**15**	**11 (73.3)**	**11 (73.3)**	**11(73.3)**	**14(93.3)**	**-ive**	**-ive**	**10(66.7)**	**13(86.7)**	**12 (60)**	**9 (60)**
5 (1.0g/kg MH)	**11**	**11 (100)**	**9 (81.8)**	**10(90.9)**	**10(90.9)**	**-ive**	**-ive**	**5 (45.5)**	**9 (81.8)**	**5 (45.5)**	**6 (54.5)**

- TH and MH showed a potentiating effect on the expression of pro-apoptotic proteins Apaf-1= Caspase 9, p53 and IFNGR1.
- TH and MH showed a lowering effect on the expression of anti-apoptotic proteins Bcl-xL, TNF-α, COX-2 and ESR1compared to non-treated positive control.

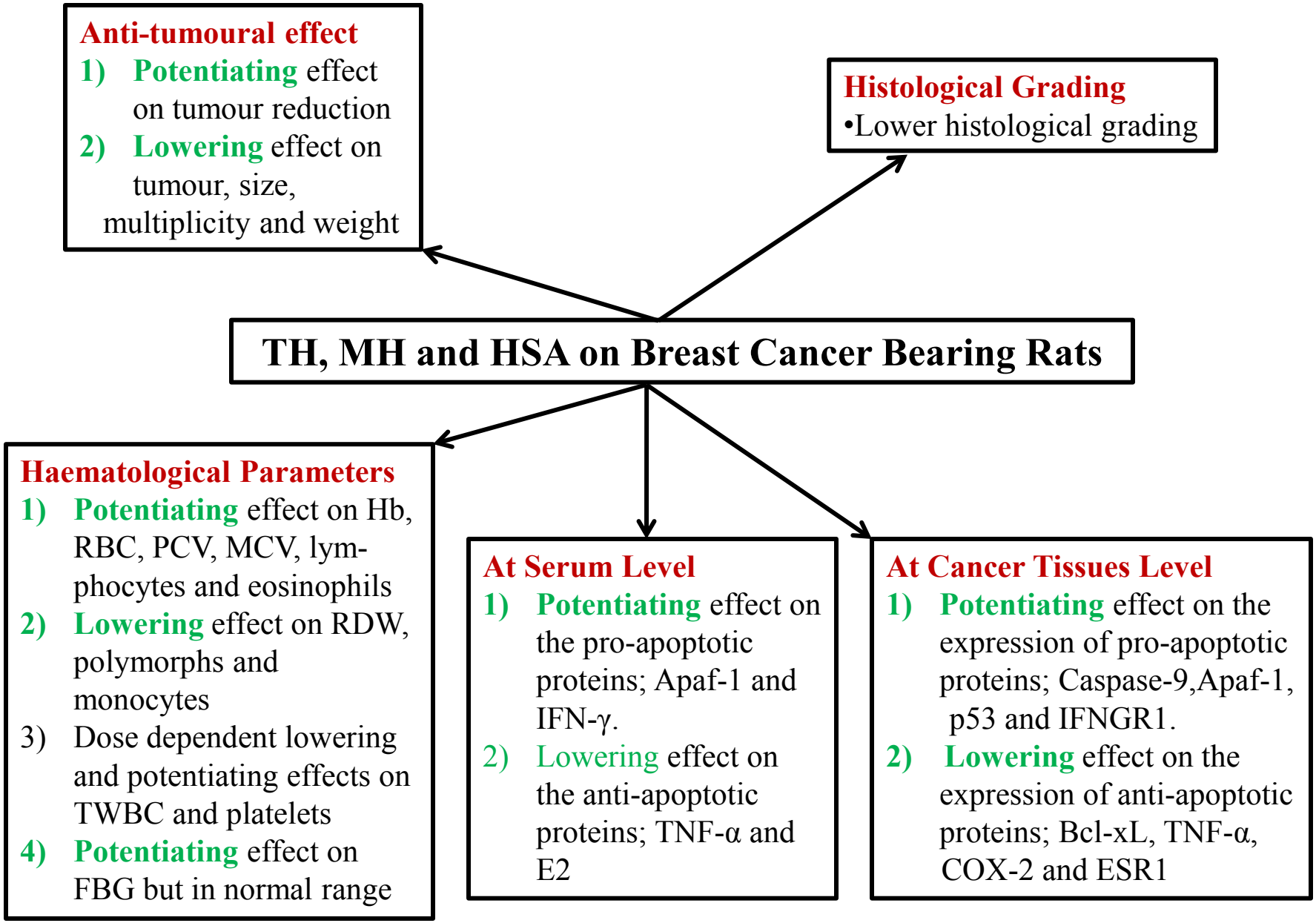
Immunohistochemical Expression (%) of Pro and Anti-apoptotic Proteins at Cancer Tissues level (Honey treatment started AFTER cancer is palpable

Tumours		No. of positive tumours (% expression or positivity)									
Group	**Total**	**Caspase9**	**Apaf-1**	**P53**	**IFNGR1**	**FASLG**	**FADD**	**Bcl-xL**	**TNF-α**	**COX-2**	**ESR1**
1 +ive control	40	**12 (30)**	**15 (37.5)**	**17 (42.5)**	**20 (50)**	**15 (37.5)**	**13 (32.5)**	**31 (77.5)**	**30 (75)**	**26 (65)**	**32 (80)**
2 (0.2g/kg TH)	25	**17 (68)**	**18 (72)**	**13 (52)**	**18 (72)**	**-ive**	**-ive**	**12 (48)**	**17 (68)**	**12 (48)**	**16 (64)**
3 (1.0g/kg TH)	23	**16(70)**	**15(65)**	**14(61)**	**17(74)**	**-ive**	**-ive**	**11(48)**	**17(74)**	**11(49)**	**14(61)**
4 (2.0g/kg TH)	30	**21 (70)**	**17(57)**	**22(73)**	**22(73)**	**-ive**	**-ive**	**13(43)**	**21 (70)**	**13(43)**	**17(57)**
5 (1.0g/kgMH)	30	**21 (70)**	**19(63)**	**20(67)**	**25(83)**	**-ive**	**-ive**	**13(43)**	**22(73)**	**13(43)**	**17(57)**
(1.0g/kgHSA)	25	**18 (72)**	**15 (60)**	**17 (68)**	**19 (76)**	**-ive**	**-ive**	**13 (52)**	**18 (72)**	**13 (52)**	**17 (68)**

- **TH, MH and HSA showed a potentiating effect on the expression of pro-apoptotic proteins; Apaf-1= Caspase 9, p53 and IFNGR1.**
- **A lowering effect on the expression of anti-apoptotic proteins; Bcl-xL, TNF-α, COX-2 and ESR1compared to non-treated positive control.**

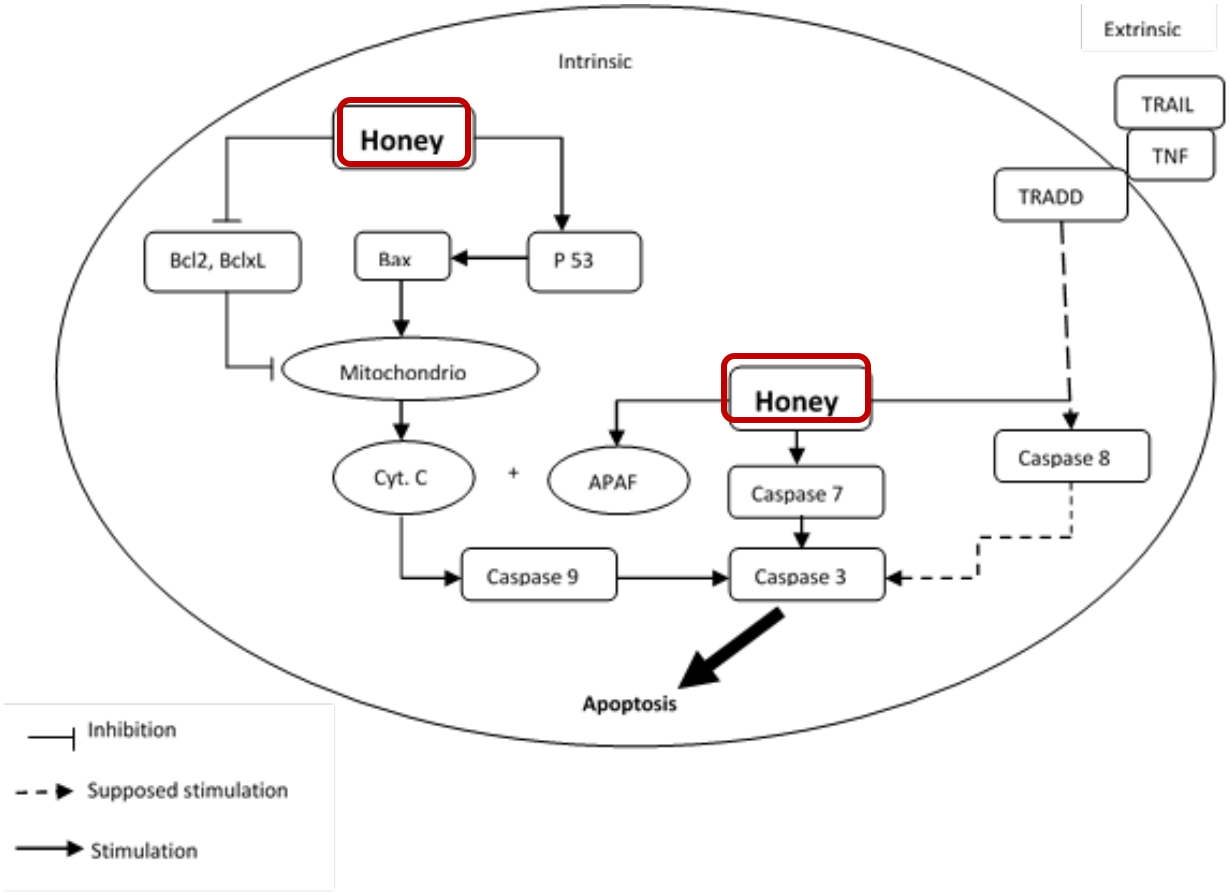


Summary of results (honey treatment started **BEFORE** cancer induction).



Summary of results (treatment started **AFTER** cancer is palpable).

Mechanism of anti-apoptotic pathway of Honey

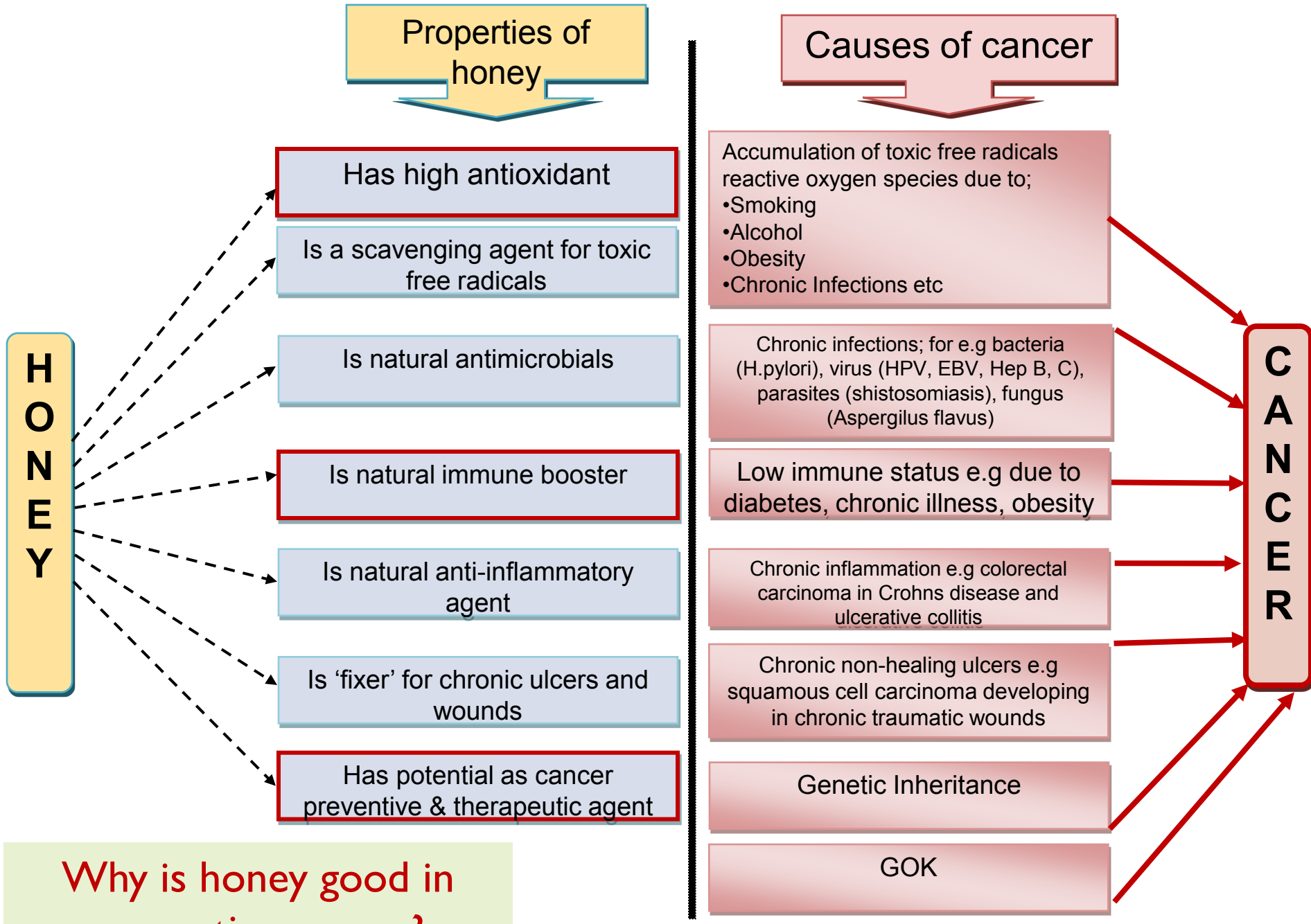


Legends: Bcl-2 — B cell lymphoma 2; BclxL=B cell lymphoma extra large; Cyt. C — cytochrome C; APAF-1 — apoptotic protease activating factor 1; TNF — tumor necrosis factor; TRAIL — TNF related apoptosis-inducing ligand; TRADD — TNFR associated death domain protein.

Ref: Oxid Med Cell Longev. 2018 Jan 18;2018:8367846. doi: 10.1155/2018/8367846. eCollection 2018

CONCLUSION OF HONEY STUDY

1. **Honey when given 7 days BEFORE tumour induction and given AFTER breast cancer development**
   1. Decreases tumour size, weight, multiplicity and potentiates latency
   2. Has better histological grading
   3. Improves hematological profile
   4. Increases the expression of pro-apoptotic proteins (Caspase-9,Apaf-1, p53, IFN-γ and IFNGR1) at serum and cancer tissue level
   5. Decreases expression of anti apoptotic proteins (Bcl-xL, TNF-α, COX-2, E2 and ESR1) at serum and cancer tissue level
2. **The mechanism by which TH and MH exert cancer-preventive and cancer-therapeutic effects is multifold; through**
   a) Modulation of immune response by ameliorating haematological and serological parameters, and
   b) By activation/modulation of pro and anti-apoptotic proteins of intrinsic pathway at serum and tumour tissues levels
3. **Honey could be used as possible natural 'preventive' agent against breast cancer,**
4. **Honey could be used as adjuvant to chemotherapy**



Why is honey good in preventing cancer?

Publications on Honey study

•*Honey and Cancer: Sustainable Inverse Relationship Particularly for Developing Nations—A Review.. Evid Based Complement Alternat Med. 2012;2012:410406. Epub 2012 Jun 17*

•*Does Honey Have the Characteristics of Natural Cancer Vaccine?. Journal of Traditional and Complementary Medicine 2 (2012) 276-283.*

•*Review on the Medicinal Effects of Tualang Honey and Its Comparison With Well Established Manuka Honey. Malays J Med Sci. May-Jul 2013; 20(3): 6-13.*

•*Inhibitory Effect of Tualang Honey on Experimental Breast Cancer in Rats: A Preliminary. Asia Pacific Journal of Cancer Prevention; 2013,14(4),2249-2254 DOI:http://dx.doi.org/10.7314/APJCP.2013 14.4.2249*

• *Honey as a Potential Natural Anticancer Agent: A Review of Its Mechanisms, Evidence-Based Complementary and Alternative Medicine, vol. 2013, Article ID 829070, 7 pages, 2013. doi:10.1155/2013/829070.*

•*Inhibitory effects of Malaysian tualang honey and Australian/New Zealand Manuka honey in modulating experimental breast cancers induced by n-methyl-n-nitrosourea (mnu): A comparative study. Pathology. 2016 Feb;48 Suppl 1:S148. doi: 10.1016/j.pathol.2015.12.403.*

•*The Anti-Cancer Effects of Tualang Honey in Modulating Breast Carcinogenesis: An Experimental Animal Study. BMC Complimentary and Alternative Medicine; 2017 Apr 11;17(1):208. doi: 10.1186/s12906-017-1721-4.*

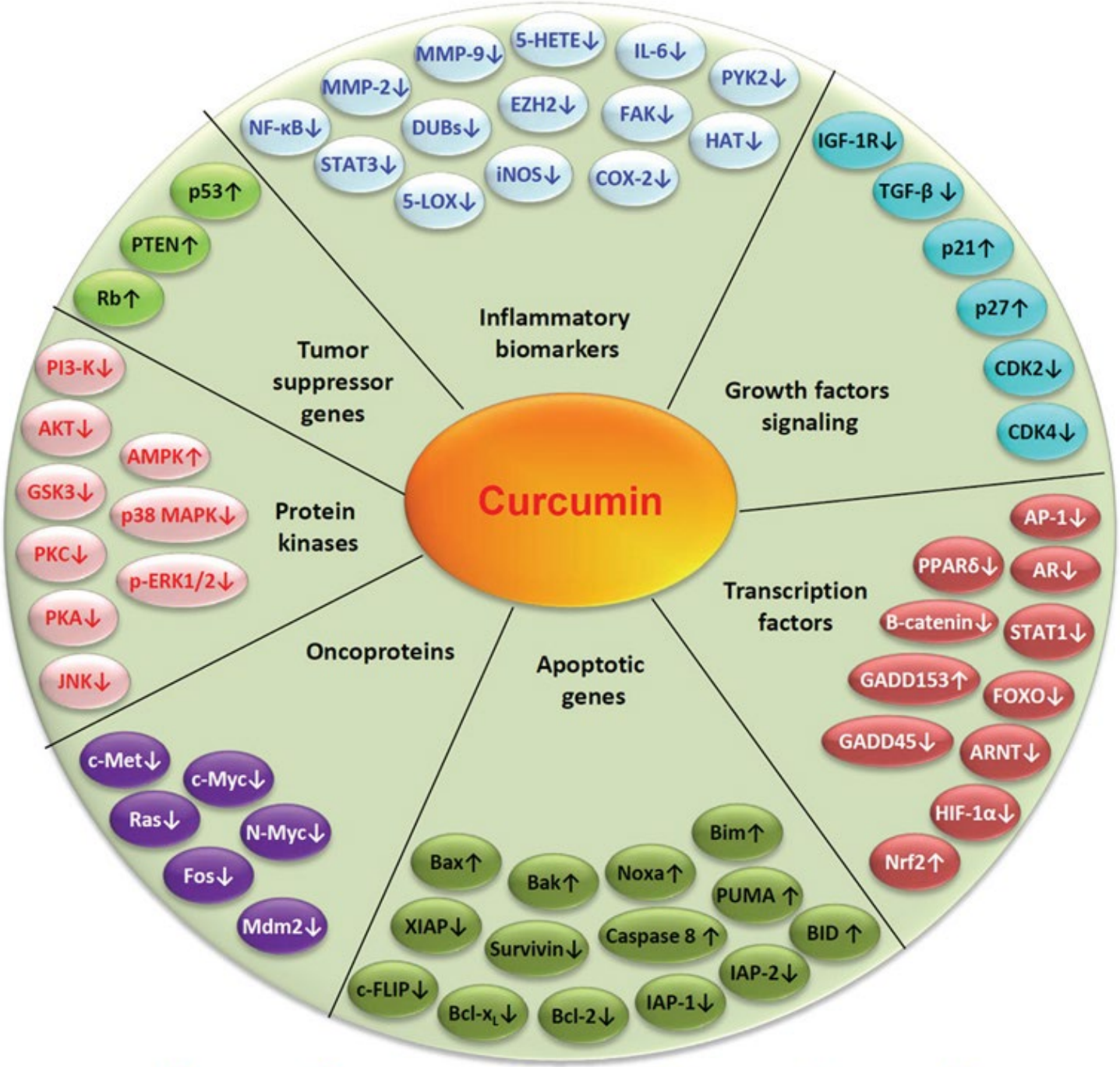
•*Oral Administration of Tualang and Manuka Honeys Modulates Breast Cancer Progression in Sprague-Dawley Rats Model. Evid Based Complement Alternat Med. 2017;2017:5904361. doi: 10.1155/2017/5904361. Epub 2017 Apr 5*

•*Honey As a Potential Natural Antioxidant Medicine: An Insight Into Its Molecular Mechanisms of Action.. Oxid Med Cell Longev. 2018 Jan 18;2018:8367846. doi: 10.1155/2018/8367846. eCollection 2018.*

•*Effect of Daily Supplementation of Malaysian Jungle Tualang Honey and Australian/New Zealand Manuka honey on Hematological and Some Biochemical Variables in Female Rats.. Annals of Life Sciences 2 (5) (2018) (10-22).*

•*Effect of Apis Dorsata Honey and Honey Sugars Analogue on Hematological and Some Biochemical Parameters in Albino Rats Model.· Asia Pacific Journal of Science and Technology: Volume: 23. Issue: Volume: 23. Issue: 02. Article ID.: APST -23-02-07..*

Vaccine 5: Curcumin


Curcumin
Inflammatory biomarkers
MMP-9↓
5-HETE↓
IL-6↓
PYK2↓
MMP-2↓
EZH2↓
FAK↓
HAT↓
NF-κB↓
DUBs↓
STAT3↓
iNOS↓
COX-2↓
5-LOX↓
Growth factors signaling
IGF-1R↓
TGF-β ↓
p21↑
p27↑
CDK2↓
CDK4↓
Transcription factors
AP-1↓
PPARδ↓
AR↓
B-catenin↓
STAT1↓
GADD153↑
FOXO↓
GADD45↓
ARNT↓
HIF-1α↓
Nrf2↑
Apoptotic genes
Bim↑
Bax↑
Bak↑
Noxa↑
PUMA ↑
XIAP↓
Survivin↓
Caspase 8 ↑
BID ↑
IAP-2↓
c-FLIP↓
Bcl-xL↓
Bcl-2↓
IAP-1↓
Oncoproteins
c-Met↓
c-Myc↓
Ras↓
N-Myc↓
Fos↓
Mdm2↓
Protein kinases
AMPK↑
p38 MAPK↓
p-ERK1/2↓
PI3-K↓
AKT↓
GSK3↓
PKC↓
PKA↓
JNK↓
Tumor suppressor genes
p53↑
PTEN↑
Rb↑
Inflammatory biomarkers
Growth factors
Transcription factors
Apoptotic genes
Oncoproteins
Protein kinases
Tumor suppressor gene

Summary

- Cancer is on the rise
- There are natural cancer vaccines
  - Reduce your risk factors
  - Watch what you eat – sugar is sweet poison
  - Take honey and curcumin daily
  - Exercise 30min everyday
- Prevention is better than cure…. avoid smoking, obesity, stress, alcohol, be physically active →*InsyaAllah* could lead to long healthy life!