

# Red & cured meat and colon cancer: Should we become vegetarians, or can we make meat safer?

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## Conflict of Interest & Fundings

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- Other authors declare no conflict of interest
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HemeCancer Project ANR-2005-2009  
SécuriViande Project ANR-2011-2014

INRA (Nat. Inst. Agronomical Res., France)

DGER-ENVT (Nat. Vet. School, France).

Agence Nationale de la Recherche





**WARNING: HOT DOGS CAN STRIKE YOU OUT—FOR GOOD**

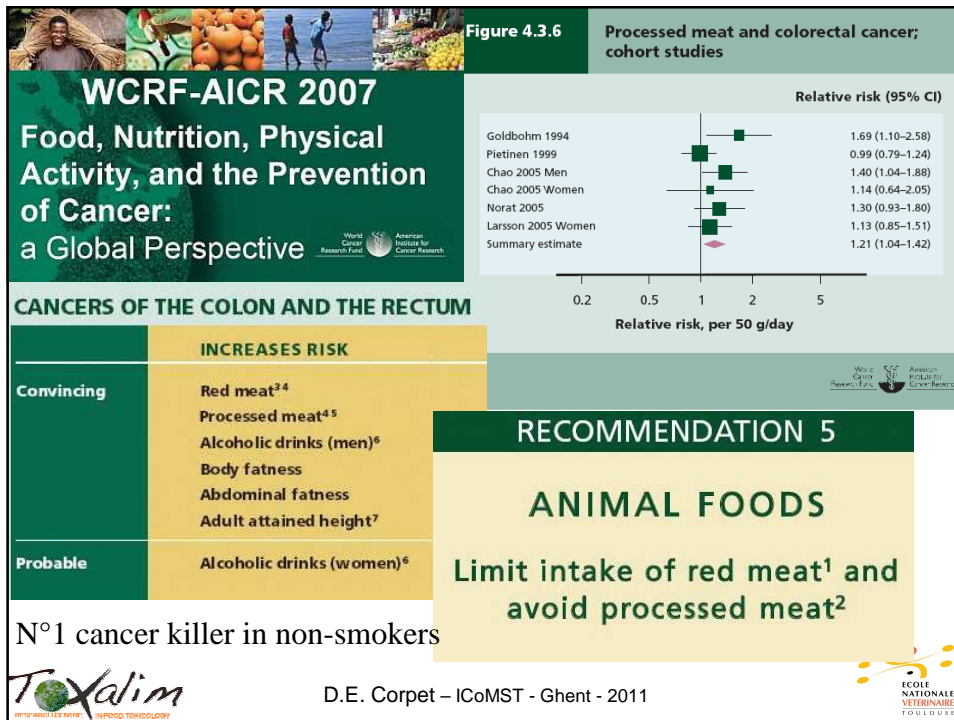
[www.CancerProject.org](http://www.CancerProject.org)



## Eating Meat Promotes Cancer

Go Vegan 

# Is this true?



World Cancer Research Fund American Institute for Cancer Research

**Continuous Update Project**  
**WCRF & AICR - May 2011**

- The WCRF-AICR Continuous Update Project Panel agreed that the recent evidence was consistent with the conclusion of the Second Expert Report (2007):
- Red meat and processed meat are convincing causes of colorectal cancer.
- Recommendations for meat eaters are
  - to limit fresh red meat intake to **less than 500 g/week**
  - to avoid processed meat (**0 g per week**).

Toxalim

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ECOLE NATIONALE VÉTÉRINAIRE FLOREUSE

Meat intake is not the only lifestyle factor that modulates colorectal cancer

### Summary estimates of Relative Risk (RR)

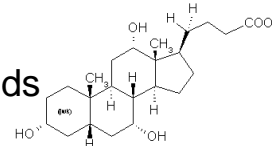
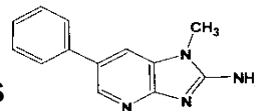
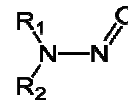
from cohort studies meta-analysis (WCRF 2007)

Factor	Evidence strength	RR	Signif.	Percent change	per
● Abdominal fatness	++	1.30	*	+ 30%	0.1 W-to-H
● <b>Red meat</b>	++	<b>1.29</b>	*	<b>+ 29%</b>	<b>100 g/d</b>
● <b>Garlic</b>	+	<b>0.73</b>	*	<b>- 27%</b>	<b>high vs. low</b>
● Alcohol	++	1.27	*	+ 27%	30 g/d
● Smoking	++	1.25	*	+ 25%	ever vs. never
● <b>Processed meat</b>	++	<b>1.21</b>	*	<b>+ 21%</b>	<b>50 g/d</b>
● Body fatness	++	1.15	*	+ 15%	5 kg/m <sup>2</sup>
● <b>Dietary fiber</b>	+	<b>0.90</b>	*	<b>- 10%</b>	<b>10 g/d</b>
● Adult attained height	++	1.09	*	+ 9%	5 cm
● <b>Milk</b>	+	<b>0.94</b>	NS	<b>- 6%</b>	<b>serving/d</b>
● <b>Calcium</b>	+	<b>0.95</b>	MS	<b>- 5%</b>	<b>500 mg/d</b>

Evidence strength:  
 ++ Convincing  
 + Probable

## Five Hypotheses on Meat & Colorectal Cancer

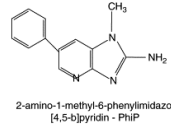
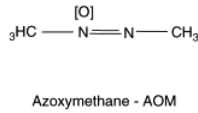
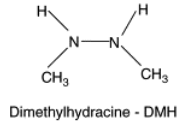
- H1- Red meat contains myoglobin with **heme iron**
- H2- Cured meat contains nitrate & nitrite => **N-nitrosated compounds (NOC)**
- H3- Cooking at a high temperature => **Heterocyclic Aromatic Amines** and Polycyclic Aromatic Hydrocarbons
- H4- **Fat** => excess calories & bile acids
- H5- Meat may lack protecting agents (e.g., calcium, phytochemicals)



The relative importance of heme iron, nitrate & nitrite, and HCAs and PAH on CRC burden appears to be roughly equivalent, according to three recent cohort studies. But epidemiology cannot provide true evidence. Experimental studies are needed to prove that a cause produces an effect, and to understand mechanisms

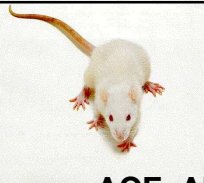
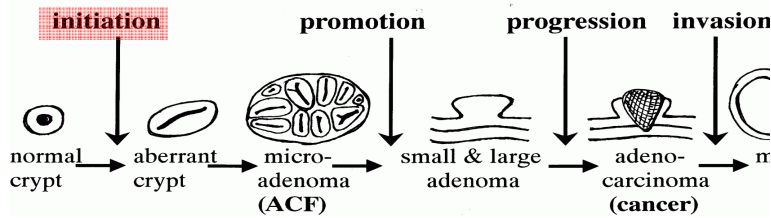
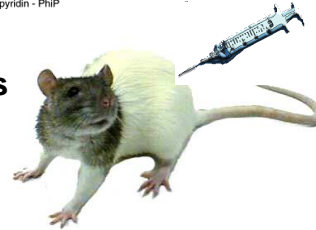
## Method: Rats given a colon carcinogen

DMH, AOM, PhIP, MNU, MNNG...



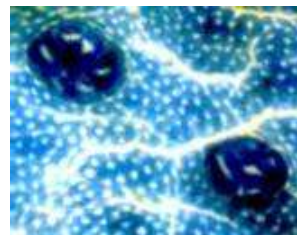
No spontaneous colon cancer in rats  
but **easy to induce ACF, MDF & cancers**

Tumor development & pathology  
are similar in rats and in humans

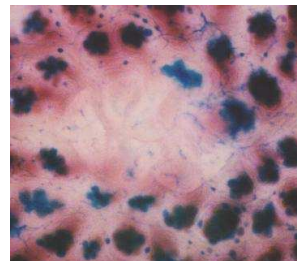


## Rat model with precancer lesions

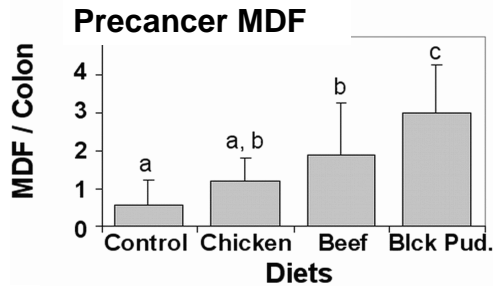
**ACF, Aberrant Crypt Foci**  
Methylene Blue staining x40,  
15d after carcinogen initiation  
Correlation with cancer, not 100%  
(Bird, Cancer Let. 1987)  
Ki-ras mutation



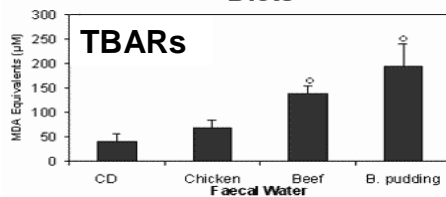
**MDF, Mucin Depleted Foci**  
HIDAB staining x40 high iron diamine Alcian blue  
100d after carcinogen initiation  
MDF-cancer correlation >> ACF  
(Caderni, Cancer Res. 2002)  
Apc mutation (Femia, 2007)



## Rat Model → First evidence of red meat & heme promotion of colon carcinogenesis:



In a calcium-depleted diet, Beef meat & Black pudding (blood sausage) promote Mucin Depleted Foci (& ACF)  
More heme = more MDF

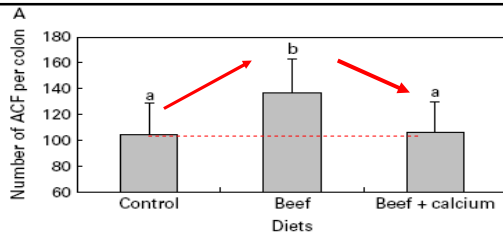


Beef meat & Black pudding raise fecal & urinary markers of fat peroxidation: TBARs, DHN-MA, cytotoxicity  
More heme = more peroxides

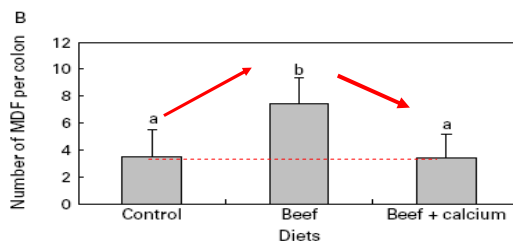
Pierre et al., J.Nutr. 2004



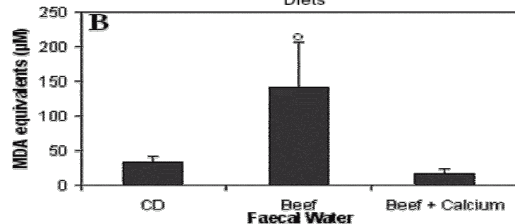
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**Dietary Calcium normalizes beef meat effects**



**=> Calcium fully suppressed beef-induced promotion**



Fat peroxides: MDA genotoxic & cytotoxic

**=> Calcium fully suppressed beef-induced lipoperoxidation**

Pierre et al., British Journal of Nutrition (2008)

## MECHANISMS

### *Apc* mutation induces resistance of colonic cells to liperoxide-triggered apoptosis induced by faecal water from haem-fed rats

F.Pierre<sup>1,\*</sup>, S.Tache<sup>1</sup>, F.Guéraud<sup>2</sup>, A.L.Rerole<sup>1</sup>,  
 M.-L.Jourdan<sup>3</sup> and C.Petit<sup>1</sup>

<sup>1</sup>Ecole Nationale Vétérinaire Toulouse, UMR INRA-ENVT Xénobiotiques,

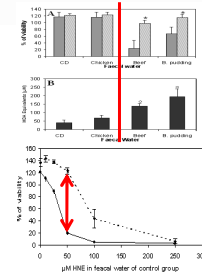
Published mechanistic studies suggest that heme-induced fat peroxides promote colon cancer by **selection of *apc* mutated cells** in the colonic mucosa

In all our previous rats studies, carcinogenesis promotion by meat or heme was associated with fat peroxidations biomarkers:

- Fecal water TBARS
- Fecal water cytotoxicity
- Urinary DHN-MA (metabolite of 4-hydroxynonenal)

*Pierre et al., 2003, 2004, 2006, 2007; Santarelli et al., 2008*

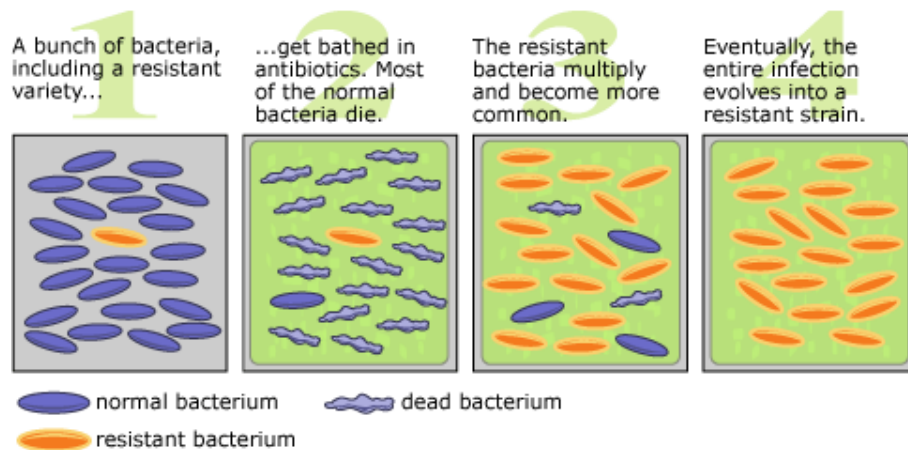
The agents that decrease the level of these biomarkers also suppress carcinogenesis in rats



### How can haem & liperoxides promote cancer?

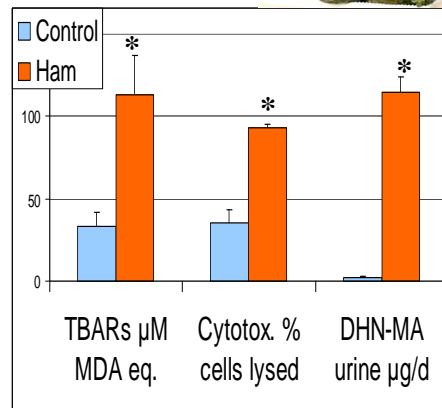
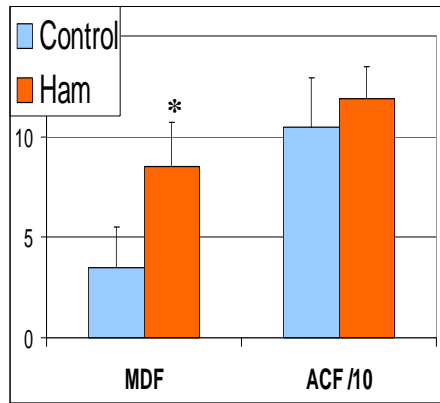
We guess it is by **selection** of cancer cells

Similar to selection of drug resistant bacteria by antibiotics



## Freeze-dried oxidized cooked ham

given to initiated rats promotes precancer MDF and increases markers of lipoperoxidation & cytotoxicity



Pierre et al., Nutr. & Cancer, 2010

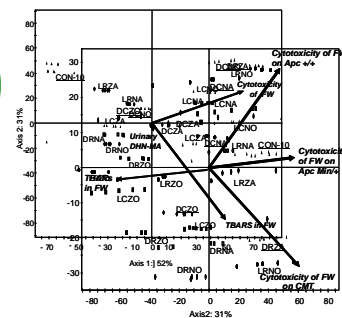


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## Design of a short-term study in rats given 16 models of cured meat

16 processes	Anaerobic packaging	Five day air exposure	Added Nitrite
Dark meat shoulder	DCZA DCNA	DCZO DCNO	DRZO DRNO
Light meat langiss. dorsi	LCZA LCNA	LCZO LCNO	LRZO LRNO
	Cooked 70°C Raw 50°C	Cooked 70°C Raw 50°C	Zero ppm N 150 ppm



Principal component analysis of biomarker data, to choose 4 cured meat models → 100 d carcinogenesis study

Short-term study of 2x2x2 factors = 16 models of cured meat.  
End-points: Early fecal and urinary biomarkers used as screening tools



Dark Cooked Nitrited Oxidized = DCNO  
 Dark Raw Zero-Nitrite Oxidized = DCZO  
 Dark Raw Zero-Nitrite Anaerobic = DRZA  
 Dark Cooked Nitrited Anaerobic = DCNA  
**Given for 100 days to carcinogen-initiated rats**



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**Meat Processing and Colon Carcinogenesis: Cooked, Nitrite-Treated, and Oxidized High-Heme Cured Meat Promotes Mucin-Depleted Foci in Rats**

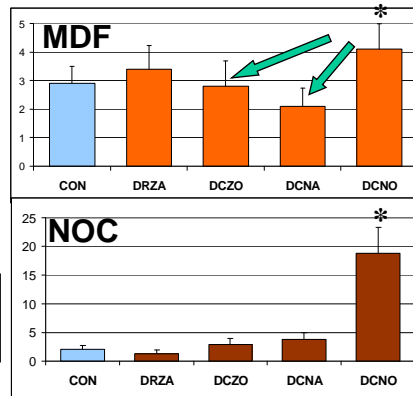
**Cancer Prevention Research**

Raphaëlle L. Santarelli<sup>1,2</sup>, Jean-Luc Vendevre<sup>2</sup>, Nathalie Naud<sup>1</sup>, Sylviane Taché<sup>1</sup>, Françoise Guéraud<sup>1</sup>, Michelle Viau<sup>3</sup>, Claude Genot<sup>3</sup>, Denis E. Corpet<sup>1</sup>, and Fabrice H.F. Pierre<sup>1</sup>

DCNO model cured meat (Dark, Cooked, Nitrite-treated and Oxidized high-heme meat) promotes colon carcinogenesis and increases fecal end products of lipid peroxidation in rats (Santarelli et al., *Cancer Prevention Research*, July 2010).

But if No Oxygen or No Nitrite  
 DCNA & DCZO → No promotion

Fecal N-nitrosated compounds clearly associated with promotion

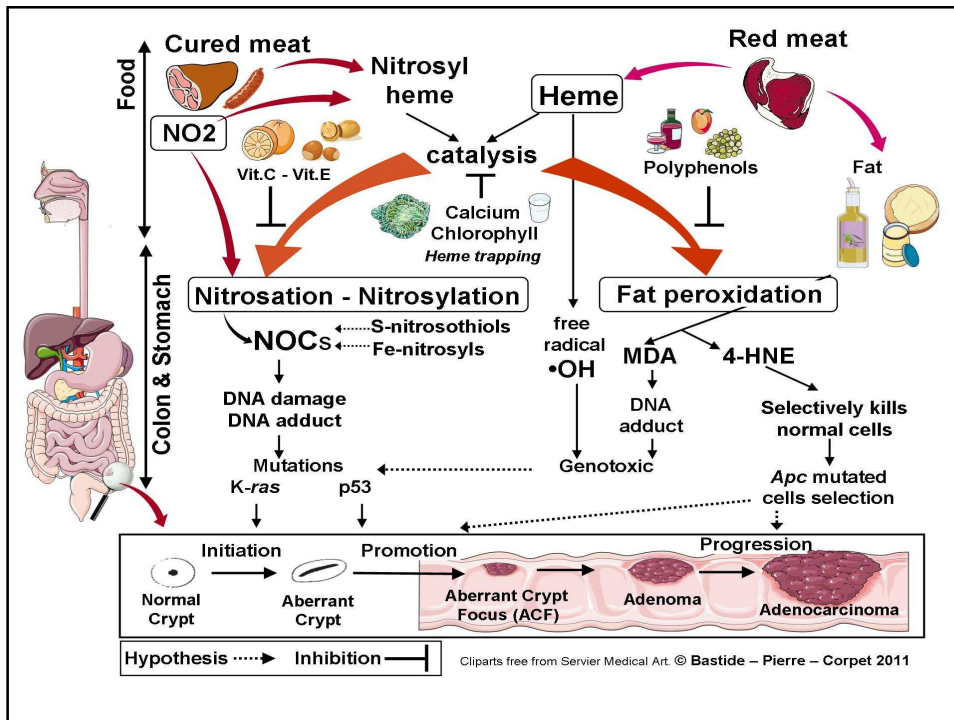


Effect of a cured meat diet on MDF and NOC formation in the colon of rats 106 days after carcinogen injection (values are means ± SD, n = 10. \* significantly different from control P < 0.05)



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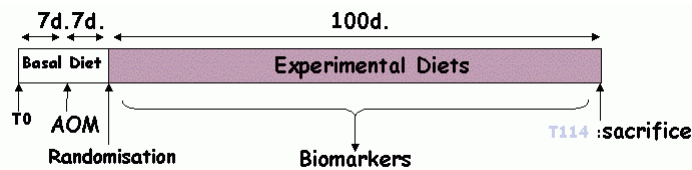




## Unpublished Prevention Study in Rats

**Aim:** to **prevent** the promoting and pro-oxidant effects of cured meat with a heme iron binding-additive or an antioxidant-additive.

**Calcium** carbonate (150µmol/g) or **α-tocopherol** (0.05%) added to the model cured meat diet DCNO, and given for 100 days to rats pretreated with a carcinogen. Colons were scored for preneoplastic MDF.



## Results 1: Prevention of Cured Meat MDF Promotion in Rats

In rats, cured meat DCNO increased the number of MDF/colon after feeding for 100d (p=0.01)

Full Data not shown  
before publication

Calcium and  $\alpha$ -tocopherol fully normalized the number of MDF/colon (p=0.01)

Effect of cured meat diets on MDF formation in the colon of rats 99 days after the injection of 1,2-dimethylhydrazine, (values are means  $\pm$  SD, n = 10)

\* Significantly different from CON diet (P = 0.01)

# Significantly different from DCNO diet (P = 0.01)



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## Results 2: Prevention of Cured Meat- Induced Fecal Peroxidation in Rats

In rats, cured meat increased the fecal TBARs (fat peroxides)

Full Data not shown  
before publication

Calcium, but not tocopherol, reduced fecal TBARs & cytotoxicity, and urinary DHN-MA, in cured meat-fed rats

(only TBARs data are shown)

Nitroso-compounds (NOC) assays are ongoing

Effect of cured meat diets on fecal peroxidation biomarkers (TBARs) in rats after 80 days on experimental diets (values are means  $\pm$  SD, n = 5)

\* Significantly different from CON diet, P = 0.01

# Significantly different from DCNO diet (P = 0.01)



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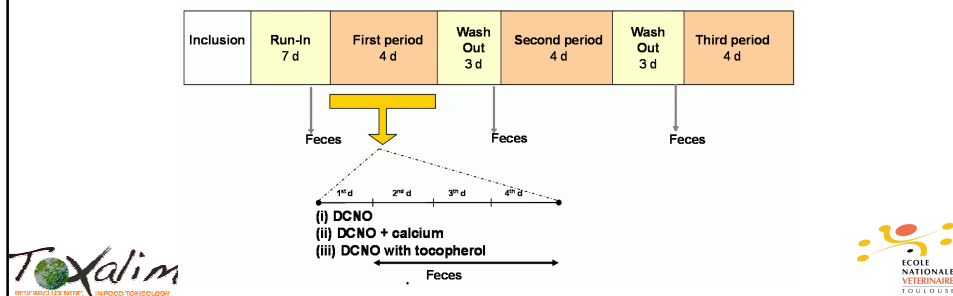




## Unpublished Prevention Study in Volunteers

- In a cross-over trial, 17 healthy volunteers were given the model cured meat (DCNO = 160g/d “ham” for 4 days), as such or supplemented with **calcium** carbonate (1g/d) or with  **$\alpha$ -tocopherol** (80mg/d).

Stool samples assayed for TBARs and NOC (ongoing)



## First human data fit rats data

**TBARs increased** in stools of 17 volunteers given cured meat compared with meat-free period (Wilcoxon  $P < 0.05$ ).

Calcium and  $\alpha$ -tocopherol supplementation fully normalized fecal TBARs in volunteers given cured meat ( $P < 0.05$ ).

Fecal nitroso-compounds (NOC, ATNC) assays are ongoing

Full Data not shown before publication

Effect of cured meat diets on fecal biomarkers (TBARs) in stools of **volunteers** after 4 days on experimental diets (values are means  $\pm$  SEM,  $n = 17$ )

\* Significantly different from meat free period,  $P < 0.05$

° Significantly different from DCNO period,  $P < 0.05$



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## Conclusion of the unpublished study

- Promotion of colon carcinogenesis in rats by cured meat (DCNO) was suppressed by dietary calcium and by  $\alpha$ -tocopherol.  
Calcium normalized associated fecal and urinary biomarkers in rats (TBARs, cytotoxicity, DHN-MA)
- Dietary calcium and  $\alpha$ -tocopherol normalized fecal TBARs in human volunteers given cured meat.
- Many people are reluctant to change their diet: the advice “*avoid processed meat*” is badly adhered to. The addition of specific agents to cured meat may provide a new way to prevent colorectal cancer... and to move towards a fair society ?

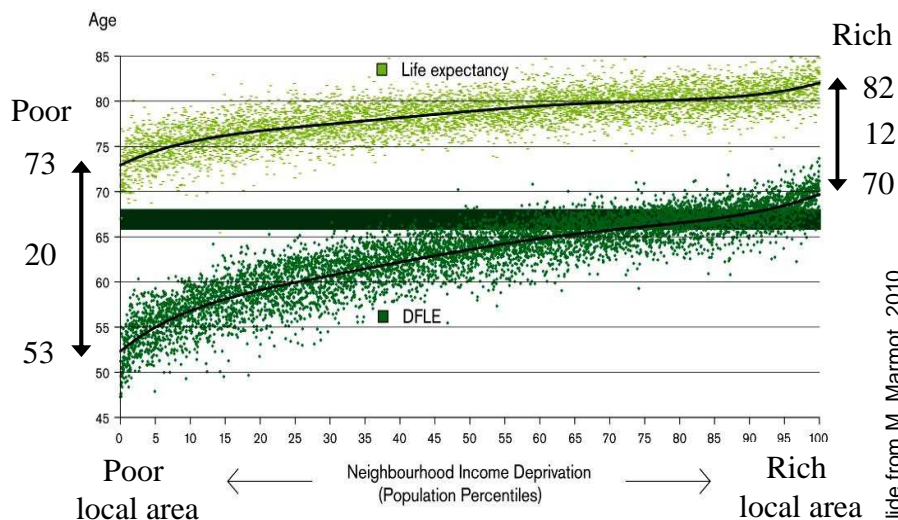


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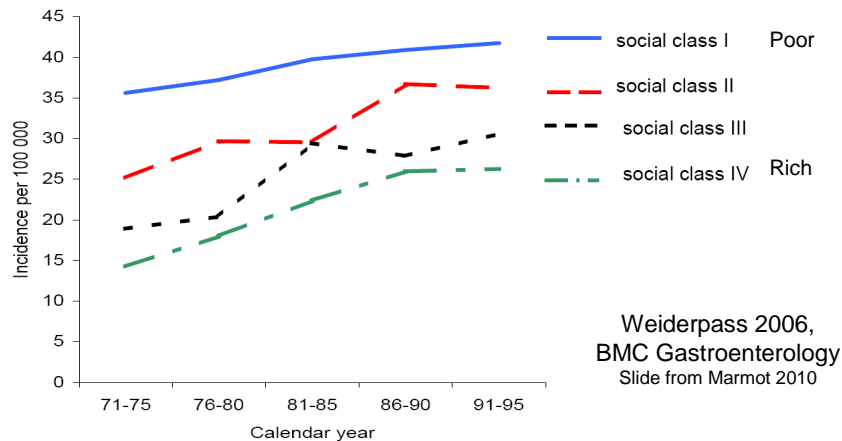
## Life Expectancy at Birth, and Disability-Free Life Expectancy (DFLE)

by Neighbourhood Income Deprivation, England, 1999-2003



## Age adjusted incidence of Colon cancers among male Finns

aged 45–64 at the beginning of each 5-years period between 1971–1995



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## Health inequalities

- The poor live shorter lives in good health than the rich. Colorectal cancer is a part of the inequality burden. Red meat & cured meat are a part of the colorectal cancer burden.
- Less educated people do not follow advices about smoking, exercise, sensible drinking and healthy eating.
- But are they really free to do so? (Marmot, 2010)
- Our responsibility is to make a safer meat:

**More ethical, an easier, to change the food  
than to change the consumer**



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# Eating Meat Promotes Cancer

Go Vegan 

Go vegan ... or make your meat safer!

Potential paths for a safer cured meat:

- Change diet (e.g., eat more calcium)
- Change process (e.g., without O<sub>2</sub> or NO<sub>3</sub>)
- Use new additives (e.g., tocopherol)

Sorry, but no recipe is available yet!



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