Is diet a bigger factor in lung cancer than smoking?

1. Abstract

Background: Cancer appears a mysterious disease as we are lacking clear explanations for 1. demographic cancer rate differences, 2. cancer rate changes over time and 3. following changes in smoking participation, differences in personal and population lung cancer risks. Potentially incorrect assumptions or beliefs are behind the mystery of cancer which might imply that our cancer prevention and treatment are suboptimal.

Aim: A better understanding of carcinogenesis at a basic level.

Approach: Conduct causality research, cancer research and a systematically review of a wide variety of associated cancer observations utilizing first principles only. In order to identify the most likely causal forces explaining all observations under consideration, evaluate the contrasts and communalities between the observations while exploring potential carcinogenic pathways. The Bradford Hill Criteria of causation are used in the final evaluation of all the findings. For brevity, the findings in this paper are limited to the lung cancer perspective.

Causality findings: The effect of causal triggers is modified by the environment in which the causal triggers operate. The implications are that we can expect a minimum of not one but two different factors influencing the outcome (the effect) of any causal trigger. This makes DNA damage as a sole driver of cancers questionable.

Research findings: One semi-experiment encountered was the recent economic development of China leading to increases in both animal food consumption and a nearly four-fold lung cancer mortality rate while experiencing a decreasing smoking trend. A second semi-experimental finding came from Finland during an animal fat consumption reduction prompted by the government combatting heart disease. This reduction in animal fat consumption was associated with a significant reduction of the relative lung cancer mortality trend of the Fins compared to other countries.

Systematic review results: Analogues with the causality findings, there appears to be not one type but two different principal carcinogenic pathways involved in lung cancer. One type being (mostly) tobacco causing mutagenic DNA damage and the other type being exogenous hormones undermining the human cancer defence system through affecting apoptosis. Apoptosis has an important role in preventing DNA damage from developing into tumours. All nine Bradford Hill Criteria for causation supply a degree of evidence for the anti-apoptotic carcinogenic pathway playing a major role in lung cancer, including strong evidence from the two human semi-experimental evidence findings under contrasting conditions resulting in contrasting results.

Conclusion: It appears that exogenous hormones from medication and diet undermine the human cancer defences and increase the likelihood of the mutagenic carcinogens from tobacco resulting in lung carcinogenesis. The findings suggest that out of these two carcinogenic factors, tobacco is the minor one while the increased cancer susceptibility caused by the anti-apoptotic carcinogenic pathway is the main factor behind lung cancer.

2. Introduction

Dr T. Colin Campbell states that the findings of the China Study combined with findings in animal experiments, form convincing evidence of animal food being the main driver of the high cancer rates in the developed world.

In chapter 3 (“Turning Off Cancer”) of his book The China Study (1), Campbell describes a variety of animal experiments demonstrating control of tumour development through diet. These experiments on both rats and mice were completed by different researchers, concern various cancer locations and involve different mutagens like aflatoxin and the hepatitis-B virus (HBV). A diet moderate or high (from wheat or soy) in plant proteins, resulted in absent or low cancer development. However, if the diet contained animal proteins like casein (from cow’s milk) or fish, cancer development was high. The consistent findings between different researchers from different countries in experiments on different animals, concerning different tumour locations and studying different carcinogens, add both strength and validity to these findings.

These findings present the perspective that in rats and mice, DNA damage from the mutagens not necessarily leads to cancers but that for DNA damage to result in tumour development, a second carcinogen of a different nature and present in animal food is required.

3. Cause and effect

If we study “cause and effect” we see the incidence triggering factors acting within an environment. The resulting effect size is determined by the interaction of the causal trigger with the environment. E.g., the effect of an earthquake can be tsunamis, mudslides, destruction of habitat or just surface tremors, all depending on the environment in which the earthquake takes place.

Similarly, Edward Jenner found that a previous cow pox infection protects against the deadly small pox. The cow pox infection changes the environment in which the small pox infection takes place, creating the effect of small pox immunity. We have known about the effects of environment modification on the small pox effects since 1796 when Jenner introduced the medical profession to the concept of immunology. Nowadays, the tool of changing the environment from the perspective of the infectious agents, has many more immunological applications.

We see the same perspective returning in the flu. While most if not all people will get infected in flu season by this very infectious disease, not everybody that is not vaccinated will get sick and not all of those that get sick will get sick to the same degree. The number of people in a population affected by the flu during the flu season appears to depend on two main factors: 1. The virulence of the virus, 2. The resistance to the virus by the individuals infected.

In the flu, small pox and earthquake effects we identified two sides: the strength of the attack and the strength of the defence against the attack. This might remind the reader of Newton's third law of motion concerning actions and reactions.

From the immunological, the flu, and the earthquake examples it would appear that a single causal factor is not the norm as the environment contributes to the effect size and sometimes the effect type.

Applying this causality perspective to the animal cancer experiments described by Campbell, we can consider the mutagenic carcinogens of aflatoxin and HBV being *causal triggers* and the casein and fish consumption factors changing the *carcinogenic environment* in which these causal triggers operate. The *effect* size in the changed environment being the degree of tumour formation. Since no clear associations have been found between casein, fish or other animal food and DNA damage, for tumour formation to take place in rats and mice, the existence of a *second non-DNA damaging carcinogenic pathway* triggered by animal food consumption needs to be considered.

But what about humans? Are the high human cancer rates on the planet influenced by a second non-DNA damaging pathway as well? And what could possibly be the mechanics behind such a non-DNA damaging pathway?

4. Human semi-experiments

Carcinogenic experiments on humans are generally not ethical and avoided. In experiments, it is the researcher that controls the experimental conditions in order to see if there are corresponding differences in outcomes. If the different conditions occur accidentally, semi-experiments are formed. Following are two human semi-experiments assessing the dietary influence on lung cancer rates. One took place in Finland and one in China.

5. Semi-experiment #1 - Finland

5.1 Introduction - Finland and heart disease

In the late 1960s Finland led the world in heart disease and in the 1970s the Finnish government encouraged the Fins to 1. Reduce smoking and 2. Reduce saturated fat intake (saturated fat = mainly animal fat).

The project was initiated in the province of North Karelia but later rolled out to the whole of Finland. The project was called the North Karelia Project (2).

During the North Karelia Project, the Fins reduced their per capita dairy butter consumption by >80%:

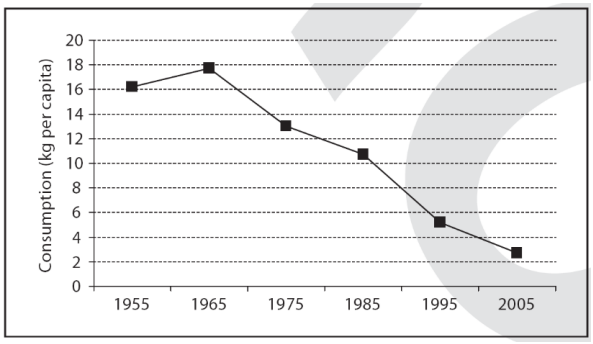


Figure 1 – The declining butter consumption per capita in Finland during the North Karelia Project

Source: Dietary Fat Quality for Optimal Health and Well-Being: Overview of Recommendations **(3)**.

The effect of the animal fat reduction on heart disease was of a similar order as the butter reduction:

Figure 2 – The changes in male 35-64-year-old heart disease mortality **(4)**

5.2 Finland – lung cancer

In the animal studies discussed before, the mutagens (aflatoxin, HBV) were considered the cancer triggers ("*the causal trigger*") and the animal food consumption regulated tumour development ("*the effect*") through changing *the environment* in which the cancer triggers operate. The animal food appeared to change the degree of tumour formation following DNA damage from the mutagens. Did the Finnish diet change also have an influence on cancer rates? E.g., did the changed environment influence lung cancer rates triggered by mutagenic tobacco?

Because of the concurrent decrease in both smoking rates and butter consumption, comparative studies involving other countries are required to supply a form of reference.

Firstly, consider the dietary habits of Japan, the USA and Finland:

Per person consumption in kg per year	***USA***	***Japan***	***Finland***
Meat	115	50	77
Fish	22	49	36
Dairy	255	72	430
Total animal food consumption	**392**	***171 (lowest)***	**543**

Table 1 – Meat, Fish and Dairy consumption in kg per capita per year in 2013

Source: Data from UN Food and Agricultural Organization (FAO) and Our World in Data (5) (6)**.**

The Japanese have a significant lower total animal food consumption than both the USA and Finland. Their traditional Buddhist beliefs discourage the consumption of animal food.

Secondly, consider the male smoking habits of these three countries:

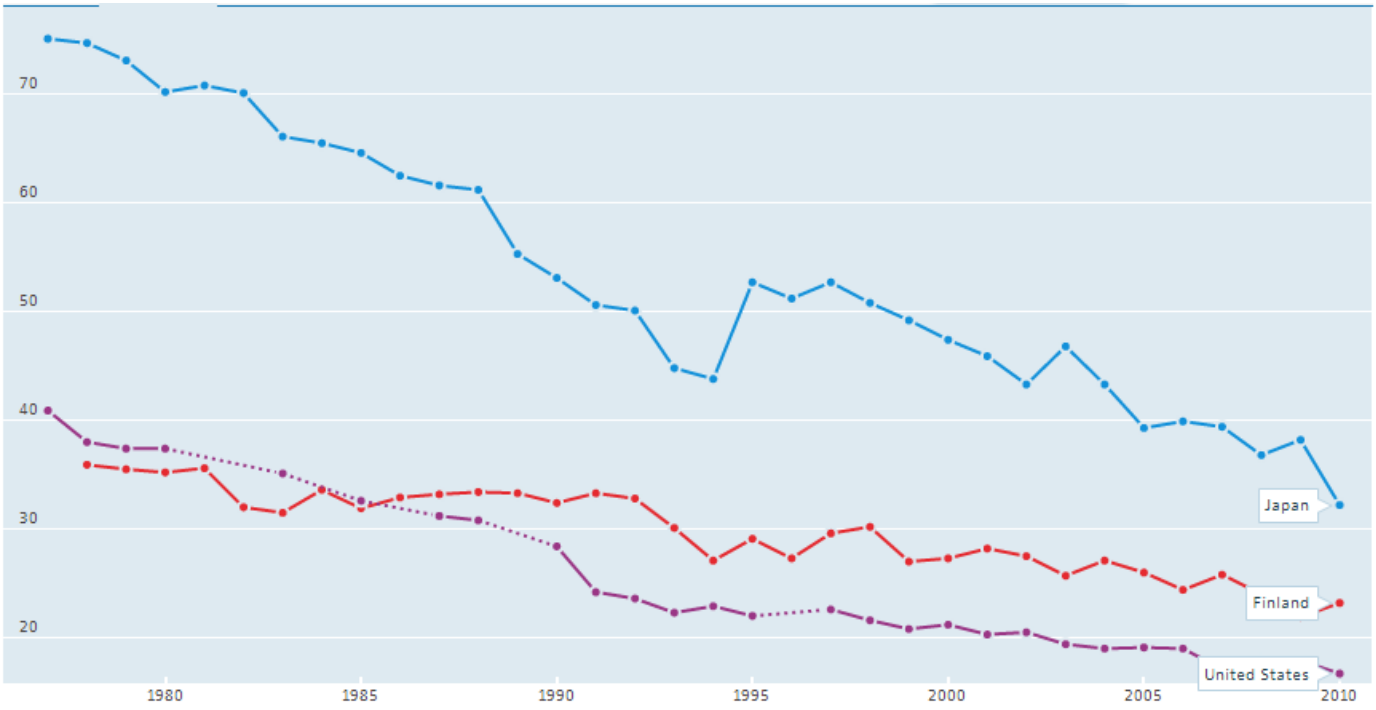


Figure 3 - Percentage of daily smokers among men aged 15+ Japan, the USA and Finland 1977–2010

Source: The Organisation for Economic Co-operation and Development (OECD) (7).

Despite the smoking discouragement by the Finnish government, the male Fins decreased tobacco consumption the least of these three countries. The Japanese tobacco consumption was consistently greater than both the US and Finland. In 1985 the USA smoking rate fell below the Finnish rate.

Thirdly, consider the Age Standardized lung cancer mortality Rates (ASR) of these three countries:

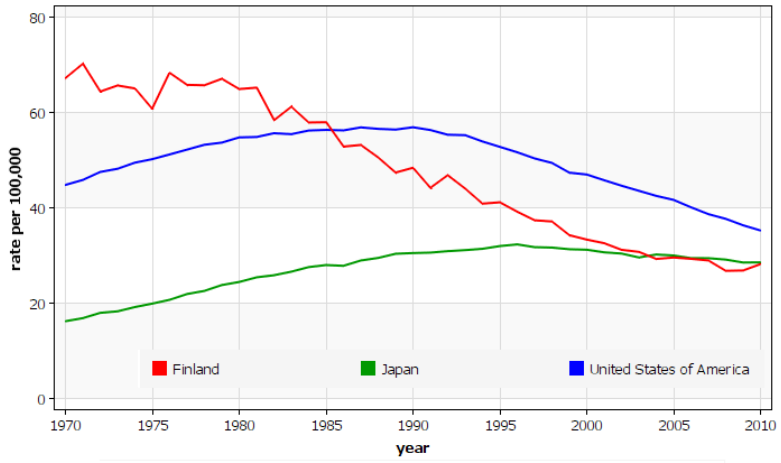


Figure 4 - Male lung cancer mortality rates trends.

Source: International Agency for Research on Cancer (IARC, part of WHO, the World Health Organization) 21.1.2020 (8).

The Japanese lung cancer mortality rates (green) were consistently lower than those of the USA (blue). In 1985 the Finnish lung cancer mortality rates (red) fell below the USA to eventually reach the lowest of the three countries.

5.3 Discussion – lung cancer trends Finland

Japanese men smoke significantly more cigarettes than the Americans but despite smoking more, the Japanese have lower lung cancer mortality rates. This has been called the Japanese smoking paradox. The Japanese consume less animal food than the Americans. Analogues to the animal experiments, the lower Japanese animal food consumption potentially could be a causal factor in the Japanese having lower lung cancer rates than the Americans. How do we find out if this might be the case?

The Fins supply us with supportive evidence:

Comparative cancer rate comparisons:

- As the Fins reduced their animal fat consumption, their lung cancer mortality rates moved from the highest of the three countries to the lowest of the three.

Temporal comparisons:

- While the USA lowered its cigarette consumption to below the Finnish consumption about 1985, almost concurrently it was the Finnish lung cancer mortality rates that fell below the USA value.

Rate of change comparisons:
The angle with the horizontal indicates the rate of change.

- Although the Finnish smoking trend decreased the least of the three countries, the Finnish lung cancer mortality rates changed the fastest.

Conclusion: Potentially animal fat consumption has an influence on lung cancer rates. Considering the contrasting temporal findings, the influence might even be considerable.

Patterns of lung cancer and animal fat consumption:
With the government's encouragement, the Finnish animal fat consumption decreased significantly as we saw in *Figure 1* taking their animal fat consumption to low levels for a western country (L). The Japanese, with their low animal food consumption (*Table 1*) already had relatively low (L) animal fat consumption levels compared to western countries like the USA with a high animal fat consumption (H). *Figure 3* shows us their relative 2010 male tobacco consumption.

	Japan	***Finland***	***USA***
Relative tobacco consumption 2010	H	M	L
Relative lung cancer mortality 2010	L	L	H
Estimated animal fat consumption	L	L	H

Summary: H=high, M=medium, L=low

Table 2 – At first glance, the 2010 relative lung cancer patterns match animal fat consumption better than tobacco consumption.

5.4 Further support

5.4.1 Comparative population variations of a *male smoker's lung cancer mortality risk ratio* 1970 & 1990

Accepting that smoking is causal to lung cancer, the ratio of lung cancer mortality risk over the % of current smokers in a population provides a proxy number indicating the relative risk of a smoker to die from lung cancer. The section following will discuss some of the issues with this approach to lung cancer risk assessment in smokers.

	A	B	C	D	E	F	G
	ASR male lung cancer mortality		male+15 daily smokers		1970	1990	Variation
	1970	1990	1970	1990	A/C	B/D	F/E*100
Australia *)	41.5	41.31	45	28.2	0.92	1.46	159
Canada	40.55	55.52	49	29.8	0.83	1.86	225
Denmark	40.76	52.46	68	47	0.60	1.12	186
Finland *)	**65.59**	**37.01**	**35.9**	**30.2**	**1.83**	**1.23**	**67**
France *)	29.42	47.8	45	39	0.65	1.23	187
Germany *)	49.66	41.69	42.2	30.9	1.18	1.35	115
Ireland *)	44.53	50.12	49	31	0.91	1.62	178
Italy *)	54.96	46.84	54.3	31.9	1.01	1.47	145
Japan	16.09	30.39	77.5	53.1	**0.21**	0.57	**276**
Netherlands	65.33	67.6	75	43	0.87	1.57	180
Norway *)	20.3	31.94	51	38	0.40	0.84	211
Sweden *)	25.93	22.15	40.9	16.5	0.63	1.34	212
UK	74.01	57.48	55	31	1.35	1.85	138
US	44.69	56.78	44.1	28.4	1.01	**2.00**	197

Table 3 - the ratio of male lung cancer mortality risk over the % of current smokers in a population (E and F) and the variation over time (G).

) Because of availability: values from Australia: 1969 - 1992, Finland: 1978 -1998, France: 1967 – 1990, Germany: 1978 - 1999, Ireland: 1973 – 1993, Italy: 1980 – 2000, Norway: 1973 – 1993, Sweden: 1977 -1997.* Data from WHO **(8) and OECD **(7)**.

In this group of countries, the rate of both the male smoking and smoking trend reduction was one of the lowest:

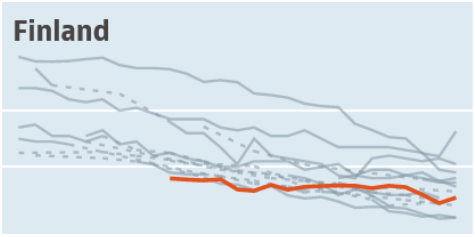


Figure 5 – Finnish male smoking rates compared to the other countries from Table 3 **(7)**.

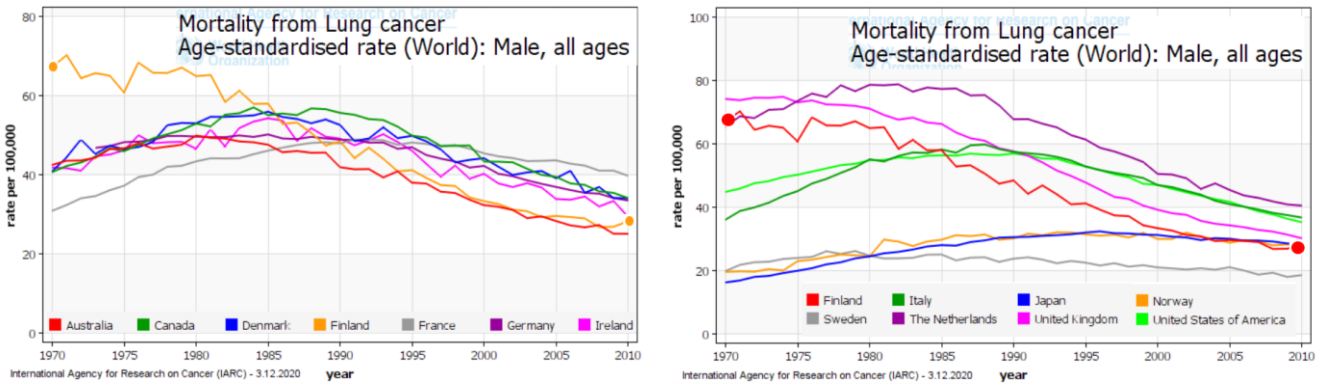


Figure 6 – Visualisation of the transition from colon A to colon B of Table 3. IARC reports the Finnish male lung cancer mortality (yellow left; red right) reducing fast (angle with horizontal) compared to most countries from Table 3 (8).

5.4.2 Discussion comparative population variations of the 1990/1970 male *smoker's lung cancer mortality risk ratio.*

In 5.2 we saw the Japanese male *smoker's lung cancer mortality risk ratio* being lower than the US and we saw the Finnish *smoker's lung cancer mortality risk ratio* changing over time while decreasing butter consumption. Potentially a *smoker's lung cancer mortality risk* changes within a few years of changing smoking habits which is what is being explored here.

The ratio of lung cancer mortality risk over the % of current smokers in a population does not differentiate between smokers, ex-smokers, non-smokers and lung cancer from other causes. The last three factors will to a degree interfere with our *smoker's lung cancer mortality risk ratio* and introduce some uncertainty. Smoking is generally accepted as the main causal factor for lung cancer which is a factor keeping this uncertainty low.

The personal lung cancer risk halving over the 10 years after quitting (9) reduces this uncertainty over time, as time will reduce the ex-smoker affect. This study aimed for a 20-year period in order to reduce the uncertainty coming from ex-smokers. For the Fins, the ex-smoker contribution to their *smoker's lung cancer mortality risk ratio* is small relative to other countries because of their lower levels of smoking and the slower smoking trend changes. This makes the validity of the Finnish *smoker's lung cancer mortality risk* measurement higher than other countries.

Hence the strength the role of tobacco in most lung cancers and the sufficiently long 20-year time interval between two readings provide strength to the validity of the *smoker's lung cancer mortality risk* measurement. The relatively low smoking rates and smoking rate changes of Finland compared to other countries contribute further validity to the Finnish findings.

Findings: Over the period of 1970-1990, the smoker's lung cancer mortality risk ratio demonstrated a Finnish 33% decrease while in the selected other countries, the average mortality risk increased by 85%.

The greatest increase in the 1970-1990 *male smoker's lung cancer mortality risk ratio* (276%) took place in Japan where the men decreased their daily smoking from about 82% in 1965 to 29% in 2018 and the 1960-1999 meat consumption increased from about 3 to 27kg per capita per year (10).

Conclusion: This observation supports animal fat consumption possibly having a significant influence on male lung cancer rates.

5.4.3 Comparative population variations of a *female smoker's lung cancer mortality risk ratio* 1970 & 1990

	A	B	C	D	E	F	G
	ASR female lung cancer mortality		female+15 daily smokers		1970	1990	Variation
	1970	1990	1970	1990	A/C	B/D	F/E*100
Australia *)	6.71	13.69	29.6	22	0.23	0.62	275
Canada	6.33	22.1	30	26.7	0.21	0.83	392
Denmark	8.73	23.83	47	42	0.19	0.57	305
Finland *)	**5.26**	**8.05**	**17.4**	**20.4**	**0.30**	**0.39**	**131**
France *)	5.03	10.16	18	24.1	0.28	0.42	151
Germany *)	5.3	10.28	16.5	18.9	0.32	0.54	169
Ireland *)	12.38	18.91	43.3	30	0.29	0.63	220
Italy *)	6.03	8.4	16.7	17.4	0.36	0.48	134
Japan	5.21	7.92	15.6	9.7	0.33	1.41	**423**
Netherlands	3.72	10.32	42	32	0.09	0.32	364
Norway *)	4.34	11.06	32	36	0.14	0.31	227
Sweden *)	6.26	12.34	32.3	21.9	0.19	0.56	291
UK	12.41	20.96	44	30	0.28	0.70	248
US	8.92	25.05	31.5	22.8	0.28	1.10	388

) Because of availability: values from Australia - 1974 and 1995, Finland - 1978 -1998, France - 1988 – 2007, Germany - 1978 and 1999, Ireland - 1972 – 1992, Italy - 1980 – 2000, Norway - 1973 – 1993, Sweden - 1977 -1997* - Data from WHO **(8) and OECD **(7)**.

Table 4 - the ratio of female lung cancer mortality risk over the % of current smokers in a population (E and F) and the variation over time (G).

5.4.4 Discussion comparative population variations of the 1990/1970 female *smoker's lung cancer mortality risk ratio*

The general discussion is under 5.4.2.

Findings: The Finnish *female smoker's lung cancer mortality risk ratio* increased the least of all countries in the list. The average increase of the other countries was 176% while Finland increased by 31%.

The greatest increase in the 1970-1990 *female smoker's lung cancer mortality risk ratio* took place in Japan (423%) where the women decreased their daily smoking from about 16% in 1965 to 8% in 2018 and the 1960-1999 meat consumption increased from about 3 to 27kg per capita per year (10).

Conclusion: The findings support that animal fat consumption possibly has an influence on female lung cancer rates.

5.5 All-cancer mortality

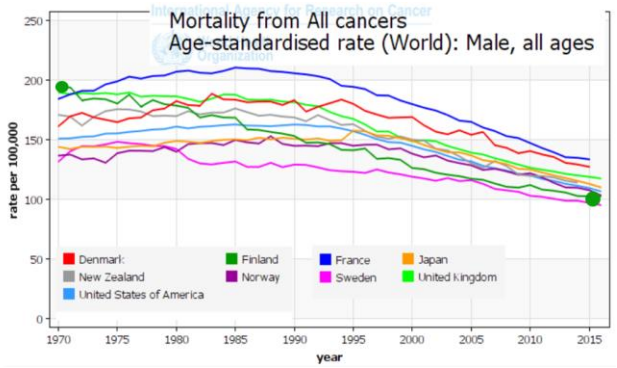
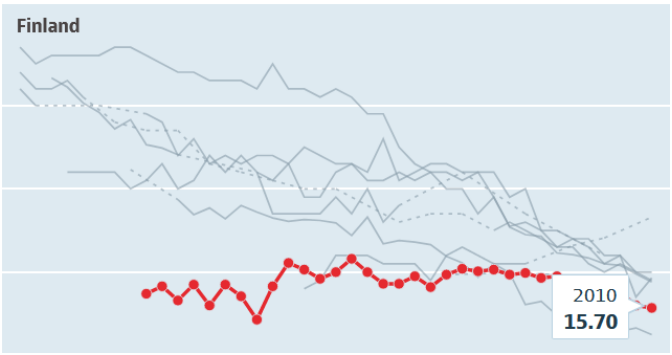


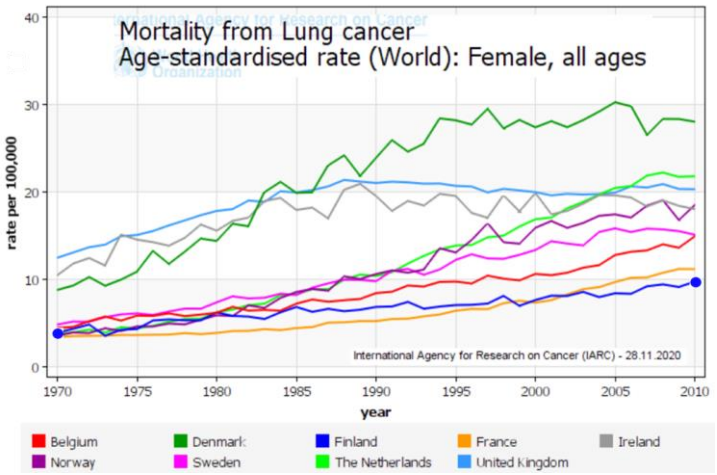
Figure 7 – The Finnish all-cancer mortality (dark green marked with dots) decreasing more than other countries.

Source: International Agency for Research on Cancer (IARC, part of WHO) 14.11.2020 (8). Apart from lung cancer reducing the all-cancer rates, the same method supports further contributions by cancer of the eye, leukaemia, thyroid, oesophagus, and cervix.

The Finnish all-cancer mortality rate reduction commencing earlier and the reduction being greater that other comparable countries, supports animal fat consumption possibly having an influence on all-cancer rates.

5.6 Female smoking and lung cancer





Left: Rate of women smokers age 15+ Finland 1970-2010 (red) compared to Belgium, Denmark, France, Ireland, Norway, Sweden, The Netherlands and the UK. The Finnish smoking trend change is among the smallest in the group. Source: OECD (7)**.**

Right: Female ASR lung cancer mortality for the same countries over the same period. Source: IARC (8).

Although the Finnish female smoking rates show a slight average increase and all others but France showed a reduction in smoking, the Finnish female ASR lung cancer rate (blue) increased the least of these countries. Again, this observation supports animal fat consumption potentially having an influence on lung cancer rates.

5.7 Conclusion:

We identified the following factors supporting that nutrition potentially has a significant effect on lung cancer rates in mostly smokers: 1. the contrasts of the USA and Japanese 1970-2010 male lung cancer trends being associated with also contrasting animal food consumption trends, 2. the Finnish lung cancer rate changes over 1970-2010 being associated with a change in animal fat consumption relative to Japan and the USA, 3. the USA male smoking rate decreasing below the Finnish smoking rates in 1985 but in the same year the Fins reduced their lung cancer mortality below the USA, 4. a decreased animal fat consumption of the male Fins being associated with a low *lung cancer mortality per % smokers ratio* compared to 13 other countries, 5. a decreased animal fat consumption of the female Fins being associated with a low *lung cancer mortality per % smokers ratio* compared to 13 other countries, 6. the fast Finnish male *all-cancer* mortality reduction trend compared to eight other countries being associated with a decreased animal fat consumption, and 7. While increasing smoking, the animal fat consumption reduction being associated with a relative small Finnish female lung cancer mortality trend change compared to eight other countries.

Furthermore, *a stronger lung cancer mortality association with the diet change than with the rate of change of the known carcinogen of tobacco* is supported by: 1. The temporality of the Finnish and USA lung cancer rate changes relative to each other contrasting smoking rate changes going in opposite directions, 2. the relative Finnish male lung cancer mortality changes

following the diet changes rather than the tobacco consumption trend, and 3. relatively low Finnish female lung cancer rate increase while increasing smoking compared to other countries decreasing smoking and achieving smaller lung cancer reductions.

Diet is potentially a more significant factor in lung cancer than smoking.

6. Semi-experiment #2 - China

6.1 Introduction – Changes

6.1.1 Life expectancy changes

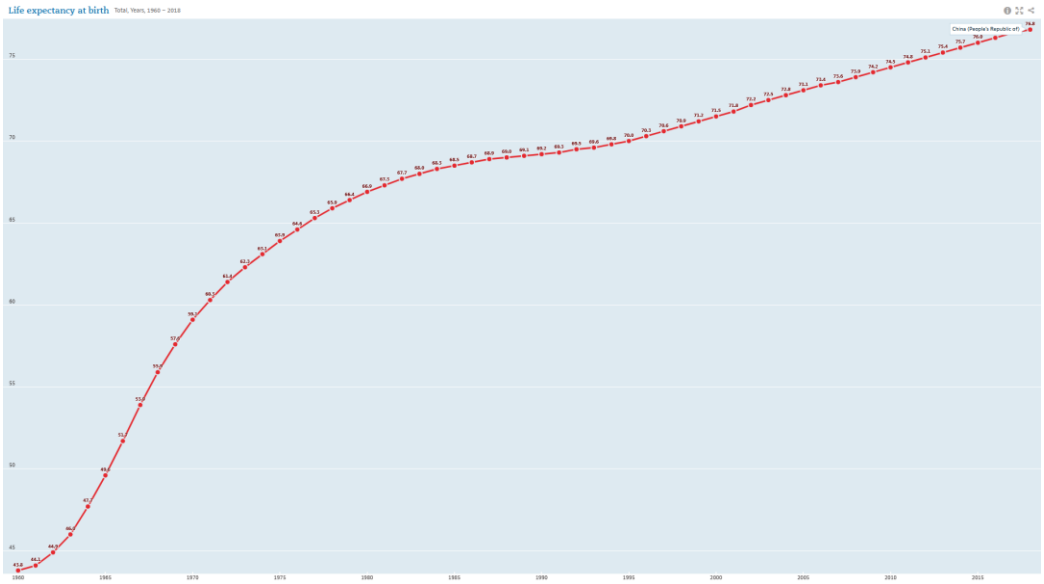


Figure 8 – Chinese life expectancy trend 1960 – 2015, Source: OECD **(10)**.

In the year 2000, the combined males and female Chinese life expectancy reached 71.5 years.

6.1.2 GDP changes

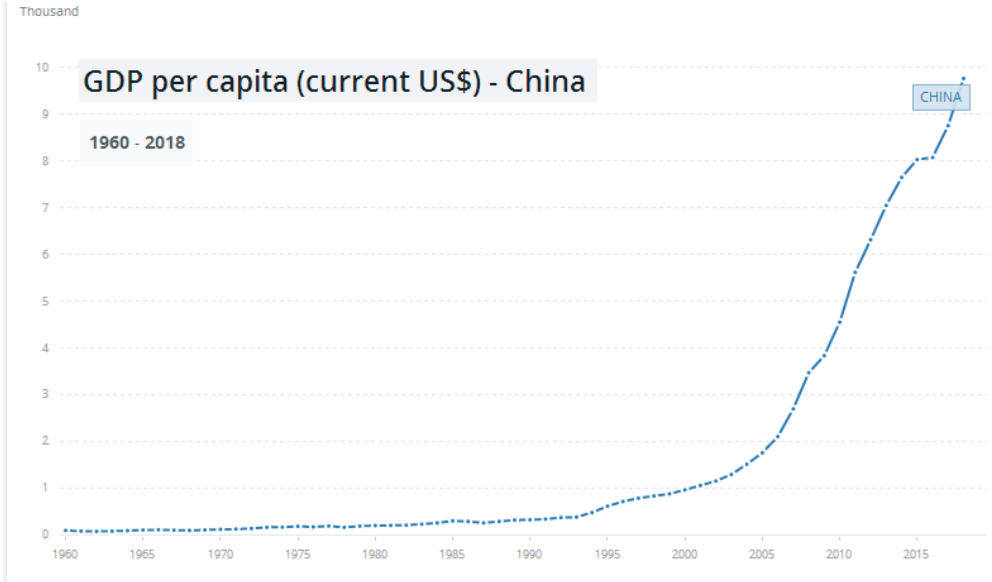


Figure 9 – Per capita income China 1960 – 2018 - Source: World Bank **(11)**.

The yearly per capita income was still under $1000 US per year in 2000 when life expectancy in China reached 71.5.

6.1.3 animal food consumption

Chinese animal food consumption in kg/capita/year:

Animal Food in Kg/capita/Year	1980	2005	% increase
Meat	13.7	59.5	***434***
Milk	2.3	23.2	***1,000***
Eggs	2.5	20.2	***800***

Table 5 – The significant animal food consumption increases in China **(12)**

From 1980 to 2005, the Chinese meat consumption increased by 434%, milk 1,000% and eggs 800%.

6.1.4 smoking trend

Male smoking in China has seen a small reduction from the 1984 value….

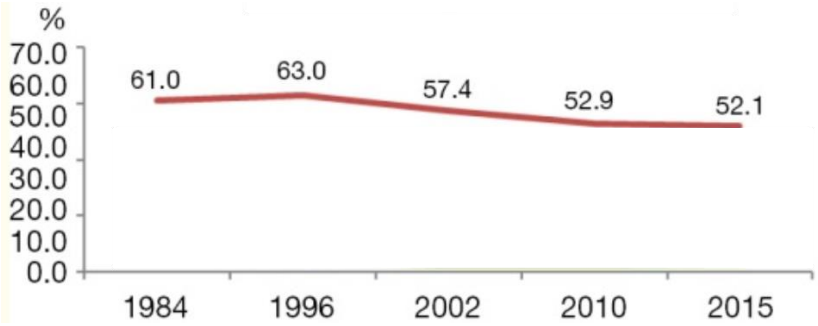


Figure 10 – Smoking prevalence among males >14 years old in China has been coming down - Source: **(13)**.

The tar delivery of the average Chinese cigarette reduced from about 27mg in 1983 to 12mg in 2010 (14).

6.2 Changes in disease rates.

6.2.1 Heart disease and Diabetes-2

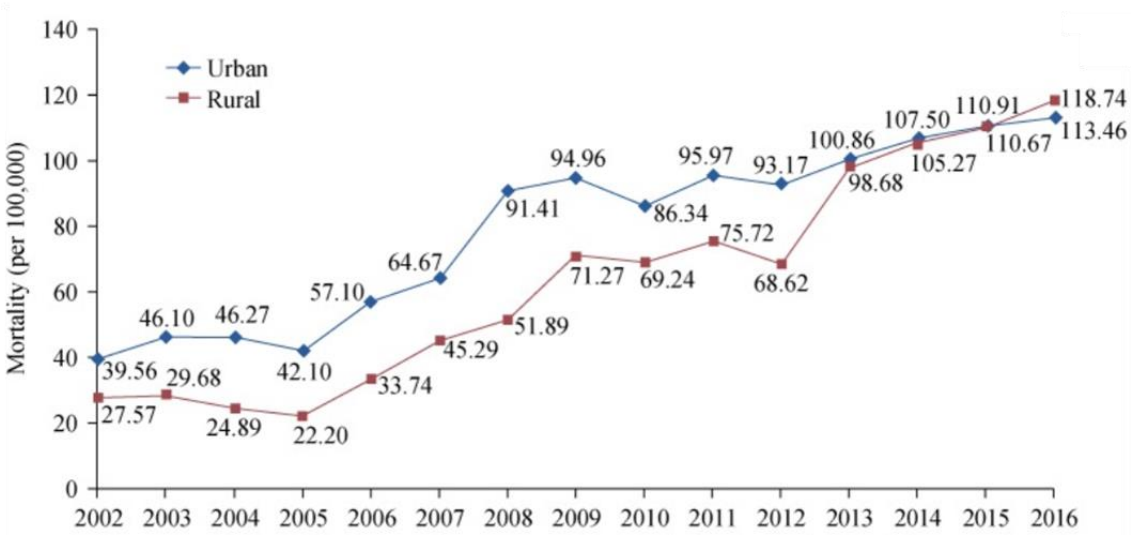


Figure 11 – Mortality rates due to cardiovascular disease in urban and rural areas in China: 2002-2016

Source: China cardiovascular diseases report 2018: an updated summary **(15)**.

While both Finland and China had small reductions in male smoking rates, heart disease decreased in Finland with the reduction of animal fat consumption and heart disease increased in China with increased animal food consumption.

A risk factor for heart disease is diabetes-2 which increased about 12-fold as the Chinese abandoned their traditional rice-based (carbohydrate) diet increasing the animal food which is much higher in fats. The Chinese before 1980 diabetes-2 rates were less than 1% (66) while in 2010 the diabetes-2 rates in China was 11.6% (67). According to one study: "the prevalence of prediabetes was 50.1%, implying that approximately 500 million Chinese adults may have had prediabetes" (68).

6.2.2 Lung cancer trend

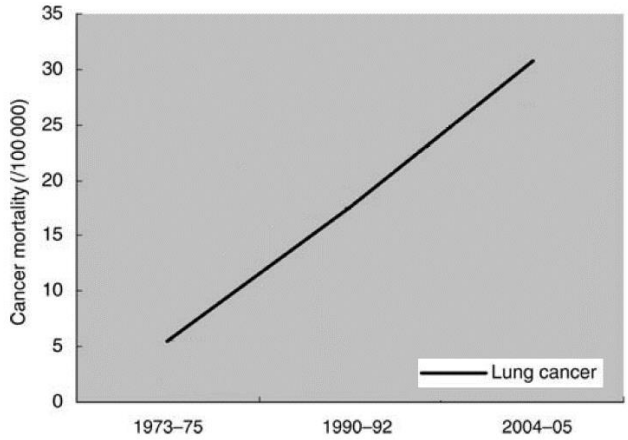


Figure 12 – China: "Lung cancer…. increased 465% during the past 30 years…" - Source: (16).

The raw (not age corrected) death rate for lung cancer for the Chinese population increased from 5.46 in 1973-75 to 30.83/100,000 in 2004/05. The Chinese age standardized rate changed from 5.6 to 20.24/100,000 over this period. Hence over this 30-year period, the raw lung cancer mortality increased 5.6 times and the age standardized rate 3.6 times (17).

6.2.3 Other cancer rate changes

- A study found a breast cancer age standardised incidence rate more than doubled from 20.01 to 44.26 per 100,000 over the 24 years from 1990–2014 in Central China (18).
- In Shanghai the age standardised breast cancer incidence rate more than doubled from 17.14 per 100 000 to 41.33 per 100 000 between 1973-2012 (19).
- As the Chinese changed their diet, in 2010 cancer became the leading cause of death in China (20).
- According to the Chinese Ministry of Health: Cancer, the major killer in today's China, represents 25% of all deaths in urban areas and 21% in rural areas (21). According to the same report, lung cancer is rising even faster than breast cancer.
- Concurrent with cancer becoming the leading cause of death, some cancer types - mostly linked to bacteria, viruses or hygiene - decreased during China's development.

6.3 Discussion - lung cancer trends in China

Lung cancer mortality increased significantly while there was a concurrent small reduction in smoking rates and a significant decrease of the tar delivery per cigarette. Further to this, there was a concurrent also significant animal food consumption increase.

The potential role of air pollution

A concurrent air pollution increase might also have influenced lung cancer rates. However, considering

- the female lung cancer mortality in Chinese selected urban areas only changed by 3% from 1987 till 2000 while being exposed to the same air as the males (8),
- The *opposite* diet associations with male all-cancer mortality rates and the heart disease mortality rates in China and Finland are coherent with the Chinese lung cancer rate increase,

it would appear that the association of lung cancer mortality with animal food consumption is more significant than the association with air pollution.

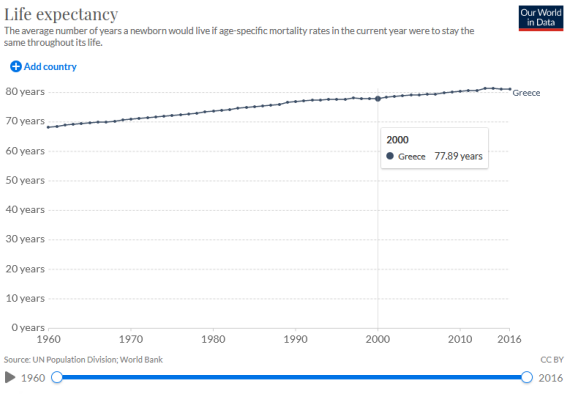
Evaluation: Support for any potential causal role of air pollution in lung cancer is moderate at best and potentially only weak.

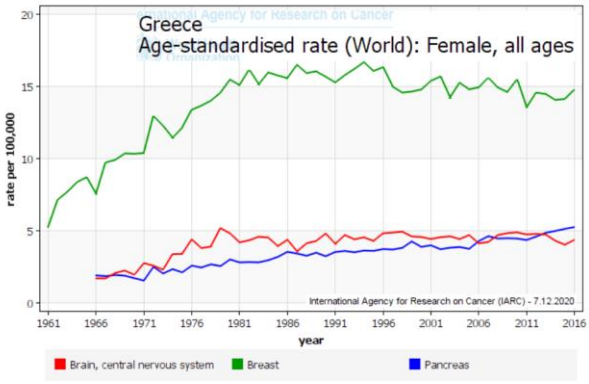
The potential role of aging

China has been aging rapidly because of the low birth rate and better living conditions. Aging increases the duration of exposure to carcinogens which will increase cancer rates. But apart from the increased exposure to carcinogens, is aging potentially a significant independent causal factor in cancers?

Consider that:

- Chinese life expectancy increased from 42.4 in 1960 to 62.5 in 1975 (20.1 years) when the lung cancer measurement started. Over the 1975-2005 lung cancer measurement, life expectancy increased by another 8.8 years. Hence the bulk of increased longevity occurred before the observed increase in lung cancer rates effectively commenced.
- Earlier we saw the Japanese male lung cancer rates being much lower than the American values despite the Japanese smoking more. The Japanese not only achieve their lower-than-USA lung cancer mortality while smoking more, they also live longer than the Americans (22).
- Longevity and cancer do not necessarily follow the same trends:





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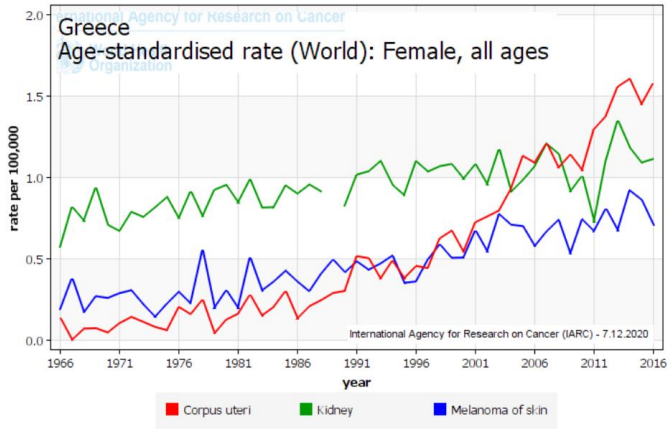

- We find a 70% less breast cancer mortality in South Korea compared to the USA while living 4.4 years longer

Country	Female life expectancy 2018 (22)	Breast cancer mortality 2010 (8)
Japan	87.5	8.98
South Korea	85.8	4.97
USA	81.4	14.36
Finland	84.6	14.66

Discussion aging as a cancer causality: While from some perspectives aging appears potentially causal to cancers and increased exposure time to carcinogens caused by aging will increase cancer rates, the other perspectives supply inconsistencies around aging and cancer rates changes and do not support aging having a significant causal role in cancers.

Evaluation: Support for a strong causal role of aging in cancers, independent of extending exposure to carcinogens, is weak however a minor role might exist.

The potential role of obesity

While the Chinese obesity rates increased concurrent with their lung cancer rates, the Finnish *male smoker's lung cancer mortality risk ratio* decreased while the % male Finnish obesity 1976-2018 increased by about 30% (24). Inconsistent lung cancer risk associations with obesity do not support obesity being a significant factor in lung cancer rates.

Evaluation: Support for any potential causal role of obesity in lung cancer is weak.

The potential role of genetics

Genetic studies indicate that the bigger variations within the human genome are among the African populations rather than among native Australian, American, Asian, European or Oceanic populations. The significant exterior differences of shapes of the eyes and skin colour are not reflected in genetic diversity (25) (26). This would imply that the likelihood of significant cancer rate changes due to genetic differences between native Australian, American, Asian, European or Oceanic populations is small.

Migrant studies do not support genetics as a significant difference causing population wide cancer rate differences. One study reported: “Studies of migrant populations, particularly the Japanese, have firmly supported the conclusions that environmental factors are of predominant etiologic significance for most major sites of cancer…” (27).

The fast increases of male Chinese lung cancer and the decreased Finnish *smoker’s lung cancer mortality risk ratio* do not support genetic changes playing an important causal role in lung cancer as it would take tens of thousands of years human for human genetic changes to occur.

Evaluation: Support for any potential causal role of genetics in lung cancer is weak.

6.4 Conclusion – lung cancer trends in China

Considering the potentially causal factors of air pollution, aging, obesity, genetics and diet change influencing lung cancer rates in mostly smokers, considering the significant increase of the Chinese all-cancer rates, considering the concurrent increase of Chinese heart disease and diabetes-2, considering the decreased tar delivery of the Chinese cigarettes, considering the results of the Finnish semi-experiment described earlier, the increase in animal food consumption appears to be the most likely main causal factor behind the Chinese lung cancer rate increase.

Since the Chinese lung cancer trend followed the diet trend rather than the decreased smoking trend or the decreased tar delivery trend of the Chinese cigarette, we can note that:

Diet is potentially a more significant factor in lung cancer than smoking.

7. Ornish’s prostate cancer RCT

In a random control trial (RCT), Dean Ornish and his group experimentally demonstrated the power of a plant-based diet in suppressing prostate cancer development (28). The researchers evaluated 1. the effects of comprehensive lifestyle changes on prostate specific antigen (PSA), 2. treatment trends and 3. serum stimulated LNCaP (androgen sensitive) cell growth, in men with early biopsy proven prostate cancer after one year from diagnosis in a random control trial containing 93 patients total. They found that none of the experimental group patients but 6 control patients underwent conventional treatment due to an increase in PSA and/or progression of disease on magnetic resonance imaging. PSA decreased 4% in the experimental group but increased 6% in the control group. The growth of LNCaP prostate cancer cells was inhibited almost 8 times more by serum from the experimental than from the control group. Changes in serum PSA and also in LNCaP cell growth were significantly associated with the degree of change in diet and lifestyle. The trial concluded: Intensive lifestyle changes may affect the progression of early, low grade prostate cancer in men.

8-16 The Bradford Hill Criteria of causation

In the sections 8-16, we will discuss the ***Bradford Hill (BH) Criteria of causation*** perspective on lung cancer: Plausibility, Strength, Coherency, Consistency, Temporality, Biological gradient, Specificity, Experiment, Analogy. These criteria were developed in the UK (with US influence) and played a strong role in determining the causal role of tobacco in diseases like lung cancer. The Bradford Hill Criteria are nowadays taught by Universities on both sides of the Atlantic. The Bradford Hill Criteria form a structure assisting in creating scientific evidence from all observations and all perspectives before evaluating all the accumulated evidence. Hence evidence is maximized while evaluation bias (prejudging) is minimized.

8. Plausibility – the anti-apoptotic carcinogenic pathway

8.1 The question has arisen how animal food consumption could possibly change the carcinogenic environment such that the tumorigenic effects of mutagenic carcinogens like aflatoxin, HBV (in rats and mice) and tobacco (in humans) are affected. In other words, how could animal food consumption make humans, rats and mice more susceptible to DNA-damaged-cells progressing into tumours? What are the possible mechanics behind damaged DNA resulting in life threatening tumours? Identifying a plausible pathway would strengthen the aggravated evidence.

In order to achieve some insights, consider the following:

8.2 The role of apoptosis in cancer prevention.

Apoptosis and mutagenic factors: Complex life on the planet has evolved in a world of mutagenic carcinogens from cosmic radiation, Ultra Violet light (UV) radiation, natural chemicals like aflatoxin from fungi, viruses, bacteria and even some carcinogenic parasites. Consequently, evolution has equipped complex life forms with tools that prevent most DNA damage from becoming life threatening tumours. One such defence mechanism is called apoptosis. Apoptosis occurs when a cell removes itself from the organism in order to protect the organism from accumulative (DNA) damage. Following apoptosis, the organism

replaces the sick removed cell with a healthy new one and the integrity of the organism has been restored, preventing DNA damage to be able to develop into life threatening tumours.

Cancer development requires on average 3 to 7 mutations according to some researchers (29). Others estimate the average number of mutations leading to a viable cancer cell to be four (30). The requirement for multiple DNA damages to *coincidentally line up to create a viable cancer cell* while concurrently apoptosis removes damaged cells, should in principle make carcinogenesis rare. Apoptosis is an important part of body maintenance and cancer prevention.

8.3 The role of hormones in cancer development. Further consider these World Health Organization (WHO) findings:

- In monograph 100A the WHO evaluates estrogen-only menopausal therapy to be carcinogenic to humans (Group 1) because of the definite associations with ovarian, endometrium and breast cancers (31).
- In monograph 91 the WHO evaluates combined oral estrogen-progestogen contraceptives as carcinogenic to humans (Group 1) because of their definite association with increased risks for cancer of the breast, the cervix, and the liver (32).

In other words, exogenous versions of the hormones estrogen and progestogen have been found to be definitely carcinogenic causing 1. Ovarian, 2. Endometrial, 3. Breast, 4. Cervical and 5. Liver cancers. Note that these reproductive hormones also have been found to be definitely causal of liver cancer which is a non-reproductive organ. Also note that menopausal therapies and oral contraceptives mostly follow the same oral pathway as our food does.

8.4 The potential role of hormones in lung cancer development. Apart from these exogenous hormones definitely causing five different cancers, research has also associated these hormones with lung cancer:

- Anti-estrogen therapy was found to have a positive effect on the prognosis of patients with lung cancer (33).
- Multiple studies, including a review of the current knowledge around estrogen and lung cancer**,** found estrogen to be an important factor contributing to lung carcinogenesis, lung cancer growth, metastasis, and affecting the prognosis (34) (35) (36).
- A study found a 70% higher rate of lung cancer in smoking women using hormone replacement therapy (HRT) compared to non-HRT users (37).
- One study found lung cancer rate among never-smokers nearly three times as high in women compared to men also supporting a hormonal influence on lung cancer (38).
- The Women's health initiative found the following observations associated with increased lung cancer risk: 1. past oral contraceptive use for >5 years in both smokers and non-smokers. 2. In never smokers, increased parity was associated with decreased risk among parous women, whereas in current smokers, older age at first birth was associated with increased risk. The researchers concluded: "Our findings suggest female hormones may influence lung carcinogenesis" (39).

A WHO study contra arguing that exogenous hormones can play a protective role in lung cancer aetiology is discussed on p. 20 in the section on issues with statistical adjustments (11.2.2) and in a broader sense also in the preceding section (11.2.1) discussing issues with reductionist research.

8.5 Hormones undermining apoptosis. Further support for animal food consumption being a second causal factor in lung cancers comes from some hormones (those promoting growth), having been shown to suppress apoptosis which would make us more vulnerable to tumour development following DNA damage. E. g. Estrogen and progesterone have been noted to prevent apoptosis in lung(!) cancer cells (40) and estrogen likely prevents cardiomyocyte apoptosis after ischemic or oxidative stress (41). Estrogen has also been noted to prevent apoptosis in endometrial cells (42). Estrogen has an anti-apoptotic effect on cervical cells (43) and estrogen has been found to alter the thresholds for B cell apoptosis (44) (45).

8.6 Animal hormones consumption and serum hormone levels

Estrogens are fat-soluble hormones and do occur in dairy and are especially high in butter (Finland!) (46). Animal consumption might unbalance natural serum hormone levels as we can see from increased IGF-I and decreased IGFBP-3 levels found in individuals with high-risk adenomas compared with normal colonoscopy and low-risk adenomas combined (47), data from nine prospective studies confirms the strong association between raised blood hormone levels (including estrogens) and an increased chance of breast cancer (48) and men in the highest quartile of serum IGF-I levels had a relative (prostate cancer) risk of 4.3 compared with men in the lowest quartile (49).

8.7 Plant based food extending a cancer patient's life. Further evidence for the anti-apoptotic effect being a cancer pathway comes from cancer patients consuming a more plant based diet surviving longer [melanoma (50), stage III colon cancer (51), breast cancer (52) (53) (54)]. Cancer patients moving towards a more plant-based diet might be extending their life expectancy (55) (56) (57) (58).

8.8 A plausible *anti-apoptotic carcinogenic pathway* supports the role of animal food consumption in carcinogenesis

The following nine observations all support the existence of a second anti-apoptotic carcinogenic pathway separate from and different to the DNA damaging mutagenic pathway:

1. the environmental contribution to the effect size in causality,
2. different animal experiments demonstrating the influence of animal food on the development of different cancers,
3. the role of apoptosis in cancer prevention,
4. the definite role of hormones in cancer development,
5. hormones undermining apoptosis including in lung cancer cells,
6. the potential role of estrogens in lung cancer development,
7. the association of cancers with raised serum hormone levels,
8. the observations of plant-based foods possibly extending cancer patient's lives,
9. the Finnish and Chinese associations of animal food consumption with lung cancer rates

All nine different observations support the plausibility of second anti-apoptotic carcinogenic pathway, besides the mutagenic pathway.

High cancer rates are potentially caused by a hormonal imbalance following the ingestion of exogenous hormones.

Animal food consumption undermining the cancer defence system of apoptosis is plausible second causal factor in lung cancers through a changed carcinogenic environment increasing vulnerability to DNA damage developing into tumours.

Anti-apoptotic carcinogens are potentially member of a bigger family of carcinogens undermining human cancer defence systems. Estrogens and progestogens appear to be not the only hormones with an anti-apoptotic effect lowering cancer defences (59).

The BH criterion of Plausibility is supported.

9. Strengths

In both semi-experiments discussed in this paper, the influence of animal food consumption on lung cancer *appeared greater than that of the known carcinogen of tobacco* which reveals a definitely degree of strength of the lung cancer and animal food association. A stronger association increases the likelihood of causality as Bradford Hill pointed out (60).

The BH criterion of Strength is supported.

10. Coherency

Is the lung cancer and animal food association coherent with other cancer findings and findings in other disciplines? The more different findings support the same potential causality, the greater the likelihood of causality.

10.1 ***The DNA integrity copying paradox.***

It is in the interest of the continuation of the species that only undamaged DNA is copied to the next generation. It is also in the interest of the individual for DNA damage to be repaired or removed from the organism in order to prevent accumulative DNA damage to be able to result in tumour formation.

Although genetic material is mixed creating variations, within one species the same DNA is copied from generation to generation over and over again over tens of thousands of years without any significant changes to the species. The genetic evolutionary process being slow tells us that the integrity of the DNA copying process is high. This notion is further supported by mutagenic birth defects being rare (0.07% of all births (60) (61)).

This is very much in contrast with the high cancer mortality rates in the developed world (sometimes over 25% of the population) which one would expect to result in a low integrity in the DNA copying process during a single life time. Somewhere during a single life time copying process starting at birth, the next generation might be initiated. Hence, we are dealing with a copying overlap of genetic material of which one branch leads to rare mutagenic birth defects and the other branch can lead to high cancer rates.

These contrasting observations around the integrity of the DNA copying process, support that cancer development is a multistage process and that likely factors other than DNA damage, are the main drivers behind cancer development.

Related to this is also *Peto's paradox* around the observation that increased body size in different mammals does not necessarily lead to increased cancer rates or decreased longevity rates for the bigger species despite a theoretically increased chance of tumorigenesis.

10.2 Reversibility of heart disease has been demonstrated only through a fully plant-based diet indicating that animal food is a likely causal factor in heart disease. This in turn supports the plausibility of animal food also being causal to cancers. Dr Dean Ornish (62), Dr Caldwell Esselstyn (63) and Nathan Pritikin have all reported reversal of heart disease through a whole food low fat plant only diet. This is also supported in this document as both China and Finland demonstrate contrasting heart disease trends following contrasting animal food consumption trends.

10.3 Reversibility of diabetes-2 through a fully plant-based diet also supports the plausibility of animal food being a major factor in cancers. In a random control trial (RCT), a vegan truly low-fat carbohydrate-based diet made from whole plants performed better from *all perspectives* than the animal food containing diet of the American Diabetic association (64).

A confusing factor in diabetes-2 is that the regulation of blood sugar levels can also be achieved through a high fat but very low carbohydrate diet. It is the complex carbohydrates (starches) that are turned into serum glucose and hence the low carbohydrate diet regulates blood sugar levels through food intake rather than through natural insulin blood sugar regulation.

In other words, the high fat low carbohydrate addresses the symptom of increased blood sugar levels and also the symptom of insulin resistance through covering up their effects. Hence, we observe diabetes-2 being strongly associated with a high fat diet while a low-fat diet reverses the disease. The true cause of diabetes-2 appears to be a high fat diet causing insulin resistance and insulin resistance in turn causing blood sugar regulation issues. An analogy is that one can address the symptom of high fuel consumption of a car by refusing to fill up at the bowser but this does not address the cause of the high fuel consumption. It only covers up the problem of high fuel consumption.

10.4 Other changes in China are also coherent with the exogenous (growth) hormone influence on lung cancer rates:

- ***Menarche:*** In the early stages of animal food consumption increases, China's age at menarche (the age of first menstruation controlled by hormones levels) declined by more than 1.6 years over the 24 years from 1976 to 2000 (65). This is an additional factor further increasing the female life time hormone load. The point made here is that the increased exogenous hormones load from animal consumption might be both increasing cancer rates and decreasing the age of menarche.
- ***Height:*** As populations increase in height (controlled by hormone levels), their all-cancer rates increase. Taller populations tend to have higher all-cancer rates. The Chinese have been growing taller (69) (70) as their animal food consumption (*Table **5***) and all-cancer rates (20) have been increasing. The point made here is that the increased exogenous hormones load from animal consumption might be both increasing cancer rates and increase the average Chinese height.
- Fertility has hormonal influences and the Chinese male sperm counts might be going down (72), the female infertility might also be going down (73) and the interest in IVF is increasing.

10.5 Dutch melanoma mortality. The Dutch raw (not age corrected) melanoma mortality rate increased nearly 24-fold over a 65-year period (71) while the Dutch became the tallest population on the planet (72). Their pancreatic cancer mortality rate increased nearly five-fold and their kidney cancer mortality rate increased over three-fold over that period. According to the Dutch Centraal Bureau voor de Statistiek, the total meat consumption was 35.4 kg/per person per year (pppy) in 1950 and increased to around 87 in 1995 when a more stable period started. Cheese consumption went from 5.2 kg/pppy in 1950 to 18 kg/pppy in 2007 (73). Not only has animal food consumption gone up, also the animals themselves consumed have increased hormone levels through the selective breeding for growth (e.g., chickens, ducks, turkeys) and selective breeding for milk yield as both growth and milk yield are controlled by hormone levels.

Further support for the lung cancer and exogenous growth hormone perspective comes from a meta-analysis of 16 studies which concluded: “high adult height is related to increased lung cancer risk” (74). The One Million Women Study found that the relative risk for total cancer was of 1·16 for every 10 cm increase in height. Risk was statistically significant for ten sites including malignant melanoma (1·32) (75).

The increase in Dutch height, the significant increase in Dutch melanoma mortality findings and the associated increase of Dutch exogenous hormone consumption, the associations of both lung cancer and melanoma rates with height, are all congruent with animal food potentially being causal of lung cancer.

10.6 Lung cancer risk discrepancy. The exogenous hormone influence on lung cancer rates is also coherent with the discrepancy between the effects on lung cancer of a personal tobacco consumption reduction and populations reducing their tobacco consumption. The personal risk halves over the 10 years after quitting (9) while e.g., the male USA population showed no decrease in lung cancer mortality over the 45-year period after the Surgeon General’s announcement that smoking was unhealthy. During these 45 years tobacco consumption reduced by about 65% but the lung cancer mortality rate was actually up from the 1964 level over the whole period (8).

Concurrent with the USA lung cancer mortality increasing while decreasing tobacco consumption, the USA per capita meat consumption over 1940 - 2010 increased by about 70% (76), the milk production per cow more than doubled between 1970 and 2015 according to the United States Department of Agriculture (USDA) (77) and the (butter fat containing) cheese consumption 1970 - 2010 went up by 350% (78). The total dairy consumption per capita went up by 17% and butter consumption by 23% between 1975 - 2015 according to the USDA (79).

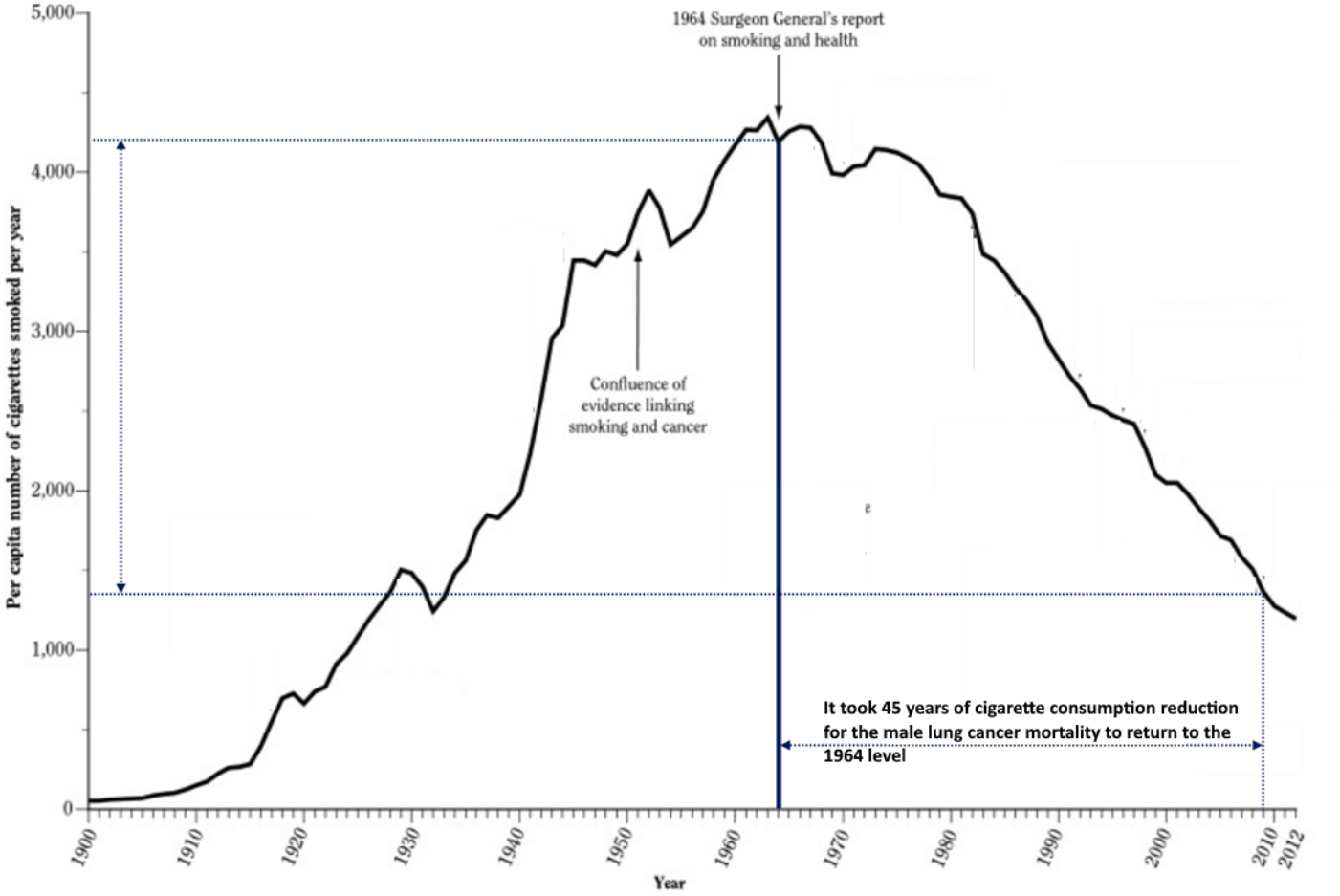

Figure 13 – It took 45 years of American male smoking reduction in order to return to the 1964 male ASR for lung cancer mortality. Adapted from **(81)**

The combined male + female lung cancer mortality in 1964 was 41.09/200,000 and despite the smoking decrease, the 2016 figure still had not returned to this value.

Year	Male	Female	Total	Comment on USA values
1964	**35.66**	5.43	**41.09**	
1990	56.78	25.05	81.83	Male peak value
1998	49.29	26.83	76.12	Female peak value
2010	**35.12**	22.99	58.11	Male value reaching below the 1964 value
2016	27.11	18.98	**46.09**	2016 total is still above 1964 value

Table 6 – After 52 years of smoking reduction, the combined USA lung cancer mortality rates still haven't returned to the 1964 levels.

Year	Male	Female	Total	Comment on Finnish values
1964	60.84	3.86	**64.7**	
1971	70.09	4.29	**74.38**	Male peak value
1984	**57.78**	6.17	63.95	Male and Total value reaching below the 1964 value
2016	22.84	10.15	**32.99**	The Total nearly halved while the Male reduction was 62%

Table 7 – After 52 years of smoking reduction, the total Finnish lung cancer mortality halved while the male lung cancer mortality rate reduced by 62%.

Sources: (80) and (8)

	1964	2009	% change
Cigarette consumption per capita USA (81)	4200	1380	67% decrease
Cigarette consumption per capita Finland (83)	1960	1200	38% decrease
M/F combined lung cancer mortality rate USA (8)	41.09	59.86	45% ***increase***
M/F combined lung cancer mortality rate Finland (8)	64.7	35.8	46% ***decrease***

Table 8 – Finnish and USA cigarette consumption and M/F combined lung cancer mortality changes 1964-2009

With a smaller decrease in cigarette consumption, Finland decreased their lung cancer mortality by 46% while a greater smoking reduction in the USA increased lung cancer mortality by 45% over 1964-2009.

10.7 Breast cancer and oral contraceptives

There is a coherency with variations of Odds Ratios of any oral contraceptive use with breast cancer incident rates is associated with the variations of the consumption of similar hormones from other sources like animal food like it is discussed on p. 22.

10.8 Conclusion coherency: Causality of the lung cancer and animal food association following the hormonal anti-apoptotic pathway is coherent with:

1. the DNA integrity copying paradox,
2. the animal food playing a likely causal role in heart disease,
3. the animal food playing a likely causal role in diabetes-2,
4. the change in the Chinese age of menarche regulated by hormones,
5. the change in the Chinese height regulated by hormones,
6. the tall Dutch increasing their melanoma mortality nearly 24-fold over a 65-year period,
7. the differences in personal and population lung cancer risks responses to variations in tobacco consumption,
8. the USA lung cancer mortality trend following the increasing animal food consumption trend rather than following the decreasing smoking trend
9. the Finnish male lung cancer mortality trend following the reduction in butter consumption,
10. variations of Odds Ratios of any oral contraceptive use with breast cancer incident rates being associated with the variations of the consumption of animal food

The criterion of Coherency is supported.

11. Consistency

If the same is observed repeatedly by different persons, in different places, circumstances and times this adds strength and validity to the evidence. Both consistencies and inconsistencies are discussed in this section. Consistency in findings strengthen the likelihood of causality while inconsistencies might decrease the likelihood of causality if they cannot be adequately explained.

11.1 – Consistencies: Is the lung cancer and animal food association coherent with other (epidemiological) findings?

- Higginson (1969, World Health Organization) calculated the proportion of cancers that were theoretically preventable and suggested that approximately 90% of all cancers in humans are influenced by exogenous factors (81).
- Higginson (1977, World Health Organization) stated that the vast majority of human cancers are due to the environment and hence are preventable (82).
- Ernst Wynder and Gio Gory (1977) state that most cancers appear to be induced by elements originating in man's environment rather than as a result of purely genetic or viral factors (83).
- The Committee on Diet, Nutrition, and Cancer, National Research Council (1982) concluded that the evidence reviewed by the committee suggested that ***cancers of most major sites are influenced by dietary patterns*** (84).
- In 1980 British *Richard Doll and Richard Peto* produced a landmark review commissioned by the US Congress Office of Technology Assessment of factors known at the time to affect cancer risk. The report's purpose was to determine the percentage of cancer of avoidable causes. The 117-page document was published in the Journal of the National Cancer Institute in June 1981.

  Summary of Doll & Peto, JNCI 1981:

Text section No.	Factor or class of factors	Percent of all cancer deaths	
		Best estimate	Range of acceptable estimates
5.1	Tobacco	30	25–40
5.2	Alcohol	3	2–4
5.3	Diet	35	10–70
5.4	Food additives	<1	−5[a]–2
5.5	Reproductive[b] and sexual behaviour	7	1–13
5.6	Occupation	4	2–8
5.7	Pollution	2	<1–5
5.8	Industrial products	<1	<1–2
5.9	Medicines and medical procedures	1	0.5–3
5.10	Geophysical factors[c]	3	2–4
5.11	Infection	10 ?	1–?
5.12	Unknown	?	?

Note that Doll and Peto estimated at that time in the USA that diet possibly was a bigger factor in cancer death than tobacco and looking at the range of their acceptable estimates diet could potentially be over double that of tobacco (85). Note also that Doll and Peto considered individual effects of individual risk factors while this paper considers the combined effect of both smoking and diet on (lung) cancer rates. Carcinogens operating through different carcinogenic pathways might not have a simple additive but a more complex multiplicative (synergetic) effect.

- The China Study (1) concluded that most cancers are caused by the consumption of animal food.

Conclusion 11.1 consistencies – There is a definite degree of consistency with some past findings.

11.2 Inconsistencies – What about inconsistencies with other (lung or other) cancer and animal food or hormonal findings?

What is different about this research for it to come up with different results?

The author encountered cancer and diet research from the last three decades to be consistently reductionist in nature, sometimes suffering from statistical data "adjustments" based on assumed causality or sometimes pooled reductionist research results in adding noise to small potential cancer signals resulting in drowning out these signals. First let's consider evidence theory:

Evidence Theory from the Bradford Hill perspective:

The convincibility of an argument depends on the Strength of the observations, the likelihood of a Plausible causal pathway, the contribution of supporting findings and any dynamic observations.

Strength and Plausibility: Strength, in the Bradford Hill sense, points at a *quantitative* (numerical) value. The higher the degree of association, the stronger the evidence as Bradford Hill pointed out. Plausibility of a causal pathway or plausible causes show us a *qualitative* characteristic which we explore through the creation of a hypothesis. Maximizing both the Strength of the association and the likelihood of a Plausibility, will give the hypothesis the greatest chance to establish a causal pathway. This happens when we peak the contrasts in the findings. Hence, evidence of causality appears when qualitative and quantitative perspectives converge on the same association. The Plausibility quality of causality can be supported by (semi) Experimental reductionist findings that might reveal a likely causal role of an agent or identify a likely causal pathway.

Supporting findings: The validity of both the qualitative and quantitative evidence might be supported or undermined by Coherency, Consistency, Specificity and Analogy with other observations. Quantitative evidence validity is increased by finding more observations (numbers) that support the hypothesis. Qualitative evidence validity is increased by finding more supporting observations done by different researchers, at different times in different places.

Dynamic observations: The evidence becomes stronger if the association can be observed under both static and dynamic conditions. Dynamic observations occur when the Biological gradient or the quantitative (semi) Experiment reveal a changing Strength of the association under changing conditions. Does the changing quality of the conditions result in changing numbers being observed? Temporality ensures that the change observed logically fits the cause-and-effect hypothesis.

Bradford Hill pointed out that a change in conditions leading to a change in the observations might reveal "the strongest support for the causation hypothesis". A change might be observed in two different directions. Observing associated changes in both directions is the pinnacle of evidence of causality.

11.2.1 Issue no. 1: Reductionism

Cancer research tends to be around individual hormones or individual food items and individual cancers while strength of an association comes from finding the perspective (hypothesis) that *maximizes contrast*. Looking at detail only, the reductionist approach, excludes the possibility of maximizing contrast; excludes finding the right perspective (asking the right question) maximizing the numerical strength of an association.

Consider the current common reductionist approach to be equivalent to researching lung cancer by brand of cigarette. The contrasting lung cancer rate of our brand of cigarette under investigation will be diluted by lung cancers caused by other brands of cigarettes. And all this happens while lung cancer is not the only type of cancer influenced by smoking which implies that there is more evidence that we are not considering. Similarly, researching the association of a particular cancer with e.g., low fat dairy, our findings might be diluted by high fat dairy, meats, fish, egg and hormonal medication and again the particular cancer under consideration might not be the perspective maximizing the strength of the evidence.

Potentially through dividing our research into 60 different types of hormones, 10,000 or so articles on the food shelves in the supermarkets and 100-200 different cancer types, we have been conquered by cancer. Through pointing our microscopes at the chlorophyll in the leaves of the trees, we might fail to see the forest.

Reductionism can potentially only contribute to the aggregated evidence through identifying the causal ***quality*** of any cancer pathway or identifying the ***quality*** of any risk factors (associations) being causal. Both of which add to Plausibility but Plausibility is only part of the total aggregated evidence. The Bradford Hill Criteria tell us that aggregated evidence includes ***quantitative evidence*** (the numerical Strength of the association) as well as ***other qualitative evidence*** including Biological gradients, Experimental findings, Coherence with other observations, Consistency among related observations, Temporality and any potential Analogies.

Limitations of reductionism:

- Reductionism does not focus on maximizing quantitative (numerical) Strength of the association; it focuses on the qualitative Plausibility criterion of the Bradford Hill Criteria.
- Reductionism might make it harder to find more complex causal relationships that are not additive but multiplicative in nature or a mixture of these two. Reductionism might make it harder to understand the interaction between multiple different causal forces displaying non-linearity.
- Evaluations done on reductionist findings only, risk evaluation bias, incorrect conclusions and confusion. It is essential that evaluations of causality include all quantitative and qualitative findings from all possible causal perspectives.

Considering the demonstrated carcinogenicity of some hormones, the maximum contrasts in cancer rates might well be between animal food containing such hormones and plant foods not containing any animal hormones. The common reductionist approach considering individual cancers, individual food items and individual hormones can only contribute limited evidence because of the reductionist nature significantly reducing strength of evidence.

Evaluation: All diet and cancer research of the last 30 years encountered by the author has been reductionist in nature which limits its potential to contribute to a better understanding of cancer as a disease.

11.2.2 Issue no. 2: Statistical adjustments

Cancer and diet or cancer and hormonal research at times compensates for known risk factors in regression analyses. Risk factors are associations and associations are not necessarily causations. If risk factors used to compensate data are causal, compensating for these known causal factors might indeed provide us with insights into potential levels of causality of the risk factor under consideration. However, if the risk factors used to compensate are not causal than “adjusting the data” will actually corrupt(!) the data… In epidemiology there will often be hundreds of associations. How do we decide which ones to use in our adjustments and which ones not? Could we be compensating multiple times for the same causal factor using different but related risk factors? Using risk factors in data compensation, without establishing causality of these risk factor first, is guessing. Without establishing causality first, the validity of results will not go beyond our study and we cannot generalize the findings.

Epidemiological cancer regression analyses commonly assume causality in their adjusting process and assumptions can lead to bad science. Exploring and having a play is great, but concluding that “something might be the case” is really the same as concluding that “something might not be the case”. If we don’t know, we don’t know and we might be better off not expressing a bias as our opinions guide focus away from facts and doing so can contribute to confusion.

We need to be careful adjusting data keeping *our focus on confirming or excluding causality*. We need lots of ideas in our pursuit of achieving an understanding but we also need to be cautious about where our ideas take us as human ideas can take us to some strange and dangerous places…

Example:

One study from the International Lung Cancer Consortium (ILCCO – IARC/WHO) investigating "*Hormone use and risk for lung cancer*" writes: "*To investigate potential associations between lung cancer and the independent variables of interest, we*

*performed unconditional logistic regression models, adjusted for **age** (<55; 55–62; 63–69; and ⩾70 years) at diagnosis or interview (for cases and controls respectively), **ethnicity** (Caucasian/non-Caucasian), smoking status (ever/never), **CSI** (continuous), **BMI** (continuous), **education** (low, medium, high) and **study (categorical)***" (86).

The aim was to investigate "*potential associations between lung cancer and the independent variables of interest*". This raises the question around causality of these *independent variables of interest*. Could these *independent variables of interest* possibly influence lung cancer rates the same way as we might be seeing from medicinal hormone use? Do the "independent variables of interest" perhaps also influence hormone ingestion? Is the scope of the question perhaps not big enough?

ILCCO adjusted for ***ethnicity, age*** and ***BMI.*** Consider that ***ethnicity*** will influence the types of food consumed as foods culturally differ. ***Age*** at diagnosis will influence the lifetime exposure to the foods consumed. ***BMI*** is influenced by food choices and hence this is a third factor around foods. We are looking at three types of data adjustments around food causing exposure to exogenous hormones from animal foods in a study that considers "*hormone use and risk for lung cancer*".

The exogenous hormone intake picture is rather complex and "*hormone use and risk for lung cancer*" is a reductionist perspective considering only hormones from medication and not from animal food consumption nor the influence of farming practices on the animal hormone levels in our food. In this reductionist perspective, we now have three different ways of adjusting for factors in the assumption that 1. the three adjustments are completely independent of each other, 2. these factors are causal, and 3. the adjustment factors do not contain non-causal associations introducing new biases.

Are these three factors really independent of each other? Is there really no common causality between ***age*** at diagnosis, ***BMI*** and ***ethnicity*** that could result in us adjusting multiple times for the same true causal factor (like diet) that hasn't been identified or ignored? What bias might we be introducing in an effort to reduce bias through adjusting multiple times for the same causal factor embedded in the risk factors used in the adjustment? What bias might we be introducing because of adjusting for non-causal associations embedded in the risk factors used in the adjustment?

ILCOO adjusted for ***age*** at diagnosis and for ***CSI***. The Comprehensive Smoking Index (***CSI***) is a measure of the lifetime exposure to tobacco but if we adjust for ***age*** at diagnosis, we also adjust the lifetime exposure to tobacco. There is an overlapping adjustment for factors linked to true causality (the smoking) that might not be independent of each other. Again, this might introduce bias in the data.

Past associations between medical hormone use and lung cancer in Western countries have been small and subtle. ILCOO efforts to be thorough might have reduced the clarity they were seeking rather than increasing it.

ILCCO concludes in their paper: "Conclusion: Our findings suggest that exogenous hormones can play a protective role in lung cancer aetiology".

Making adjustments is manipulating data, it is biasing data. It might be better to live with a known uncertainty than to risk increasing the uncertainty further through adjustments containing assumptions and associations that we might not have even identified. If we do not understand causality, we know very little and our knowledge will be insufficient to be meaningfully manipulate data without risking confusing ourselves further. Coherency and consistency add to validity to findings as Bradford Hill pointed out and the findings of *Hormone use and risk for lung cancer* are incoherent with the research discussed in this paper. For these reasons, and also the "data adjustments" explained above, the likelihood of the findings of this paper to be true might be low.

11.2.3 Issue no. 3: Pooled analysis using a reductionist perspective

In order to maximize evidence, the researcher needs to maximize contrasts in associated findings. E.g., the contrast between lung cancer rates is not by brand of cigarettes but by considering smoking and non-smoking subjects. A pooled analysis around smokers and non-smokers will increase confidence in lung cancer evidence. However, if the pooled analysis considers lung cancer rates from a particular brand of cigarettes, the occasional and weak cancer signal from this brand of cigarettes might well be swamped out when averaging the findings in a pooled analysis. In other words: ***we can lose the occasional cancer signal in a pooled analysis using a reductionist approach***.

This tells us that before we do a pooled analysis, we need to ensure that we have maximized the cancer signal first as otherwise we might actually end up hiding potential evidence. A pooled analysis without first maximizing contrast can lead to confusing findings. Or in a different way: before concluding that our protruding signal level was likely noise, we need to ensure that we don't use the noise from other reductionist cancer findings to drown out the little signal we accidentally encountered.

Pooled analyses can decrease findings in research not maximizing contrasts, while pooled analyses increase confidence in research maximizing contrasts. Pooled analyses are a two-edge sword.

This implies that asking the right question, finding the right hypothesis, finding the maximum contrast, should always precede a pooled analysis and the findings of pooled analyses might be meaningless if contrasts haven't been maximized first.

Example: ***Breast cancer and oral contraceptives***

In the table following we are comparing *Odds Ratio* findings of - any use of oral contraceptives and breast cancer of women of child bearing age or beyond - of selected countries together with their meat and dairy consumption per person per year (pppy) and their milk yield per cow per year

Country	***Odds Ratio***	***Breast cancer ASR (W) incidence rate*** (87)	pppy Meat consumption (88)	pppy Dairy consumption (88)	Milk yield in 1000 litres per cow per year (88)
Denmark	***1.15*** (89)	***88.8***	81.9	277.3	9.2
The Netherlands	***1.19*** (90)	***105.9***	89.5	341.5	6.6
7 days Adventists	***1.77*** (91)	***87***			
Malaysia	***2.5*** (92)	***47.5***	56.3	25.3	0.5
Iran	***2*** (93)	***31***	32.9	46.7	0.3
India	***9.5*** (94)	***24.7***	3.7	84.5	1.3

Table 9 – Variations of Odds Ratios of any oral contraceptive use with breast cancer incident rates is associated with the variations of the consumption of similar hormones from other sources like animal food.

Considering the association of breast cancer with only hormones from oral contraceptives and ignoring other hormone sources (and also the associations of other cancers with hormones) is a reductionist approach. In a meta-analysis, the low readings potentially caused by cancer signal from other hormonal sources (the animal food) like e.g., Denmark and The Netherlands can drown out the stronger findings of countries like India. This illustrates that we need to maximize evidence ***before*** doing any meta-analyses. The cancer noise from non-contraceptive hormonal sources from countries like Denmark and The Netherlands might be drowning out true cancer signals coming from Iran and India.

The Biological Gradient that appears in the table and the Coherence with the Chinese and Finnish lung cancer findings add strength to the existence of an anti-apoptotic carcinogenic pathway.

11.2.4 Issue no. 4: Denial or cultural blindness

IARC (WHO) evaluated meat and processed meats in October 2015 which is documented in Monograph 114. The Working Group considered the following factors potentially being carcinogenic in meat and processed meats: Haem iron, Lipid oxidation products, Heterocyclic aromatic amines, Polycyclic aromatic hydrocarbons, N-Nitroso compounds, Interactions between NOCs, haem iron and HAAs, Advanced glycation end products, N-Glycolylneuraminic acid (Neu5Gc), proposed oncogenic bovine virus.

Consider that exogenous pharmaceutical hormones were found to be carcinogenic in Monograph 91 in 2007 and in Monograph 100A in 2012. Further consider that these pharmaceutical hormones have been designed to be equivalent of mammalian hormones. From this it follows that mammalian hormones in meats and processed meats could well be carcinogenic. Excluding mammalian hormones from animal food consumption from the start might well have been an oversight blindly following the omnivorous culture of homo sapiens.

Discussion of the different results

All the research from the last three decades encountered was found to be reductionist in nature and hence had limited potential of contributing to the aggravated evidence. Furthermore, it would appear that the scientific requirement to maximize contrasts in observations in order to maximize evidence is often ignored or overlooked. The widespread human omnivorous culture might bring a cultural bias to the table resulting in not considering all evidence perspectives.

Conclusion 11.2 inconsistencies – Most, and perhaps all, cancer and diet or cancer and hormonal research is weak in evidence because of 1. Not maximizing contrast first in observations and 2. Only considering a reductionist approach. This might be guided by cultural bias sprouting from our 500,000- to 1,000,000-year-old omnivorous behaviour. Furthermore, meta-analyses of reductionist approaches not maximizing strength of evidence first, do not strengthen evidence and potentially even weaken evidence through reducing the signal to noise ratio by introducing more noise.

The criterion of Consistency is supported.

12. Temporality

Does the cause happen before, during or after the effect? This is the only essential Bradford Hill Criterion. In both semi-experiments we see the trend change in causal trigger coinciding with the trend change in lung cancer rates which implies that causality is possible.

The criterion of Temporality is supported.

13. Biological Gradient

Is there a biological gradient (dose response) in the lung cancer and animal food association? A dose response adds to the likelihood of causality.

Biological gradients can be identified in both longitudinal and cross-sectional studies but they appear differently.

In *Figure **1*** on p. 2 shows us a gradual decline in Finnish butter consumption. *Figure **4*** on p. 4 shows a gradual decline in lung cancer mortality rates in smokers. China to experienced gradual changes in both lung cancer animal food consumption. Hence, in both cases we see a biological gradient being playing out over time which means we see a longitudinal version of a biological gradient.

The criterion of Biological Gradient is supported.

14. Specificity

Is the association between animal food consumption and lung cancer stronger than other potential causal associations of lung cancer? A greater strength of association compared to other potential causes contributes to the likelihood of causality.

A summary of the evaluation the role of diet in lung cancer in China relative to other potential causes (from p. 11):

Agent	***Strength of the association***
Genetics	Weak
Obesity	Weak
Aging	Weak
Air pollution	Weak to perhaps moderate
Tobacco	Definite (from previous studies)
Animal food consumption	Association stronger than tobacco

The criterion of Specificity is supported.

15. Experiment

Bradford Hill reported that in (semi)experiments, when a change in conditions leads to a change in outcome, "the strongest support for the causation hypothesis may be revealed" (95). The reason for this is that in Experiment, the associations are concurrently seen from both static and dynamic perspectives and it is the intersection of these two that provides the strongest possible support for causality.

The Experiment is one of three perspectives that Bradford Hill and his colleagues came up with that observe a dynamic change. The Biological Gradient searches for a static observation that might reveal a longitudinal dynamic change. Temporality considers if the order in which two changes happen would support causality or not. The Experiment is the only criterion in which we look for a change in conditions being associated with a change in outcome.

This paper contains two semi-experiments of conditions changing in opposite directions resulting in opposite outcomes providing even stronger support than Bradford Hill described in his "The Environment and Disease: Association or Causation?" presentation. Further to this, the findings are supported by many different animal experiments mentioned in the introduction and Ornish's prostate cancer RCT.

The criterion of Experiment is supported.

16. Analogy

Cause and effect in cancer appears to be analogous to cause and effect in earth quakes, cause and effect in the flu and also cause and effect in immunology in that the effect size is influenced by the environment in which the causal factor takes place.

The criterion of Analogy is supported.

17. Discussion

We see opposite lung cancer mortality trends in Finland and China being associated with concurrent opposite animal food consumption trends. In both these contrasting cases, the influence of animal food consumption on lung cancer in smokers appears

considerable. This is further supported by Ornish's RCT also demonstrating the influence of animal food consumption on prostate cancer development. Prostate cancer development was influenced both in the subjects and in vitro by serum.

These human ***experiment*** results are further supported by 1. ***Animal experiments*** mentioned in the introduction, 2. The *all-cancer* mortality trends in both Finland and China also following the food consumption trend, 3. The ***plausibility*** of exogenous hormones driving the anti-apoptotic carcinogenic pathway increasing carcinogenesis through increasing cancer susceptibility, 4. The ***coherence*** with a plant only diet being optimum nutrition for both heart disease and diabetes-2, the coherence with the *DNA integrity copying paradox*, the coherence with Chinese age of menarche observations, the coherence with Chinese diabetes-2 observations 5. ***consistency*** with other epidemiological findings, 6. The essential ***temporality*** factor is present, 7. a ***biological gradient*** or dose response is present strengthening the accumulative evidence, 8. The lung cancer rates in smokers being influenced by exogenous hormones from animal food is ***analogous*** to both *cause and effect* observations and ***analogous*** to hormonal medication being causal of other cancers, 9. The ***strength*** of the association between nutrition and lung cancer appears greater than that of the known carcinogen of tobacco.

Bradford Hill pointed out that if the frequency of the associated events is affected, we might see the strongest support for causation (95) (96). Finland and China both demonstrate this frequency of associated events being affected. What's more, they demonstrate ***opposing trend associations which forms the strongest possible evidence***. Further to this, evidence of causality is supported by all nine Bradford Hill Criteria of causation.

18 Conclusion – The role of diet in lung cancer development

Considering the potential influence of diet, obesity, genetics, air pollution, and aging# on lung cancer rates, considering the severe limitations of the generally reductionist research around cancer and considering the evidence contained in this document, there is significant support for animal food being the main causal factor in lung cancer in mostly smokers.

Further:

- It would appear that exogenous hormones from animal food and medication making us more susceptible to lung cancer development through interfering with our natural apoptosis levels is a greater factor in lung cancer development than tobacco containing more than 70 carcinogens (97).
- It appears contradictive that cancer patients receive chemotherapy or radiotherapy in order to *encourage apoptosis* of cancer cells and encourage tumour shrinking and concurrently cancer patients are fed animal food *undermining apoptosis*. Plant based nutrition would appear to be optimum for both extending a cancer patient's life, achieving remission and appears to be a more important factor in cancer prevention than the cessation of tobacco consumption.
- The combined carcinogenic effects form tobacco and diet appears to be multiplicative rather than additive supporting that their carcinogenic pathways are different.

Considerations

- Animal food different in type, breed and age-consumed will contain different levels of different animal hormones likely promoting carcinogenesis of different cancers to different degrees. Further to this, exogenous hormones also come from medication. Considering potential carcinogenicity of individual factors within such a multivariate arrangement can be compared to researching lung cancer by cigarette brand. The factors not under consideration will pollute our contrasts and reduce our findings.
- The lung cancer findings of two very different carcinogenic pathways likely extend to all cancers.

19. A final word

From the cancer, heart disease and diabetes-2 perspectives discussed here, it would appear that there is a definite lack of evidence for our human omnivore behaviour (and supporting belief system) to result in optimum human health and longevity. In contrast, our belief that we are omnivores appears to cause us lots of grief and suffering. On top of this belief system we have built commercial interests influencing our research, our cultures, our understanding of our world, our education and hence the direction this world is going. The net accumulative effect of this can be seen as commercial brainwashing, maintaining and growing profits.

While reductionist findings might suit our emotional attachments to our culture, our traditions, our developed tastes, our family habits, our egos and status etc., there is a requirement for self-awareness of our very emotions feeding our greatest biases and hence our emotions being obstacles to finding the most likely truth.

Our collective nutritional and cancer sensemaking apparatus appears corrupted and faulty. We see the same corruptive forces expressed in both climate change denial and the lack of action on climate change. Climate change is taking the world towards inundations from both rising sea levels and floods and climate change also takes us towards droughts and increased soil erosion. All of these factors will reduce food production and reduce habitable land bringing us closer to WWIII and other social upheaval.

Competition fosters dishonesty and competition also fosters the hiding of the truth. At the same time, integrity, openness and honesty are at the foundations of successful cooperative societies and cultures. Successful cultures do not "just happen", we need

to work on creating and maintaining them fighting communal interests being eroded by corruptive forces only considering short-term small-scale interests. The answer to cancer is not competing over finding “the cure” but collaboratively facing the most likely truth of our behaviour being the cause. A successful culture needs to be weary of corruptive forces attempting to profit through causing confusion and aiming for a “divide and conquer”. Successful cultures have leaders with integrity aiming at the broad and long-term interests. Our current capitalist culture believing in competition and supreme human intelligence keeps us from together facing the truth about the implications of the human less intelligent collective behaviour. This stops us from reducing heart disease, cancer rates and the scary implications of climate change.

We have divided the world in “left” and “right” according to viewing responsibilities as personal or collective while it would appear that the most successful cultures built a shared collective responsibility on top of the personal one. We need the best of both worlds in order to progress on humanities most profound issues like climate change, cancer and heart disease. We need to be aware that while tens of millions of humans perished in communist Russia and China, one hundred million died prematurely between 1900-1999 from the freedom that the tobacco industry once had (98) mostly in the capitalist world. One’s freedom can be somebody else’s cost in our complex societies and complex world. The freedom to deceive others is not really justifiable if we want to advance. The clever adaptable homo sapiens can take on any survival technique found in nature, being it individualistic, cooperative, predatory, parasitic etc. but for the human race in its current cultural form to survive and thrive, the options would appear to be limited to the cooperative one.

Our emotional attachments to our differences attached to beliefs around skin colour, cultures, genders, religions, political preferences, values, morals etc. separate us from each other and distract us from collectively working on our common needs like cancer, heart disease, climate change, security, order, and a thriving community based on wisdom. It appears important to realize that our emotions can be in the way of our needs sucking us into an obsession with detail that might not even be relevant or important in the bigger scheme of things.

If we want to be selfish in a clever way, we need to contribute to and support the common good which includes science (which aims for the most likely truth) and supporting a collaborative mutual beneficial culture. Failing to be clever in our selfishness will restrict our personal outcomes. Hence be selfish and support the creation and maintenance of collective intelligence rather foster collective stupidity resulting from us trying to outsmart each other!

When the last human being on the planet dies and arrives at the Pearly Gates, Saint Peter will say: “You guys achieved some amazing feats during your rein of the planet, but if you guys had cooperated for the benefit of all, like God had suggested, you could have done so much better”.

When switching to a whole food plant-based diet, one might want to add a B12 supplement since B12 is only produced by bacteria and our hygiene and anti-biotics influence our B12 intake negatively. For optimum health avoid sugar, white flour and especially oils and any products containing them.

For a soft of this document containing the references: ***http://users.tpg.com.au/freestro/cancersummary.pdf***

For a more detailed cancer analysis and further evidence: ***http://users.tpg.com.au/freestro/cancer.pdf***

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