



Does the science support action?

5 February 2018

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World Cancer Research Fund International & University of Southampton





Outline

- Intro to WCRF
- What does the science tell us?
- Does it support action?
- Conclusion





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The World Cancer Research Fund Network







Who we are

AICR
WCRF UK
WCRF Netherlands
WCRF Hong Kong



What we do

Fund research on the relationship of diet, nutrition, physical activity and body weight to cancer risk

Interpret the accumulated scientific literature to derive Cancer Prevention Recommendations

Educate people through our national Health Information programmes



Advocate effective policies to help people and populations to reduce their chances of developing cancer





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• What sort of evidence is available?

- Trials (randomised or non-randomised)
- Cohorts
- Case control
- Ecological
- Laboratory





Hierarchy of evidence

- Meta-analysis of RCTs
- RCTs
- Non-randomised trials
- Observational
 - Cohort
 - Case-control
 - Ecological
- Opinion



Hierarchy of evidence

- RCTs
 - Good for testing discrete interventions in specific populations, over short periods
 - High internal validity
 - Questionable external validity

Observational

- Good for identifying potential aetiological factors
- Good external validity
- Subject to bias and confounding questionable internal validity







Sir Austin Bradford Hill

1897-1991





7

295

Meeting January 14 1965

President's Address

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS (Professor Emeritus of Medical Statistics, University of London)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized'.

At this first meeting of the Section and before, with however laudable intentions, we set about instructing our colleagues in other fields, it will be proper to consider a problem fundamental to our own. How in the first place do we detect these relationships between sickness, injury and conditions of work? How do we determine what are physical, chemical and psychological hazards of occupation, and in particular those that are rare and not easily recognized?

There are, of course, instances in which we can reasonably answer these questions from the general body of medical knowledge. A particular, and perhaps extreme, physical environment cannot fail to be harmful; a particular chemical is known to be toxic to man and therefore suspect on the factory floor. Sometimes, alternatively, we may be able to consider what might a particular environment do to man, and then see found. But more often than not we have no such guidance, no such means of proceeding; more often than not we are dependent upon our observation and enumeration of defined events for which we then seek antecedents. In other words we see that the event B is associated with the environmental feature A, that, to take a specific example, some form of respiratory illness is associated with a dust in the environment. In what circumstances can we pass from this

observed association to a verdict of causation? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. How such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observations reveal an association between two variables. perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?

(1) Strength, First upon my list I would put the strength of the association. To take a very old example, by comparing the occupations of patients with scrotal cancer with the occupations of patients presenting with other diseases, Percival Pott could reach a correct conclusion because of the enormous increase of scrotal cancer in the chimney sweeps. 'Even as late as the second decade of the twentieth century', writes Richard Doll (1964), 'the mortality of chimney sweeps from scrotal cancer was some 200 times that of workers who were not specially exposed whether such consequences are indeed to be to tar or mineral oils and in the eighteenth century the relative difference is likely to have been much greater.'

> To take a more modern and more general example upon which I have now reflected for over fifteen years, prospective inquiries into smoking have shown that the death rate from cancer of the lung in cigarette smokers is nine to ten times the rate in non-smokers and the rate in heavy cigarette smokers is twenty to thirty times



Inferring causality



Analysing research on cancer prevention and survival

- Strength
- Consistency
- Specificity
- Timing
- Dose Response
- Plausibility
- Coherence
- Experiment
- Analogy

Bradford Hill

World Cancer Research Fund International Global variation in cancer incidence



Stomach 154 17-154 16-63 14-66 14-00 1

Globocan, WHO, 2016

No data Not applicable



Migration data





30 25 20 Breast 15



* Per 100,000, world population standard

Hallmarks of cancer



Two enabling characteristics for acquiring hallmarks

Genome instability and mutation

1

Tumor-promoting Inflammation

Hanahan & Weinberg (2011) Cell; Hanahan & Coussens (2012) Cancer Cell

Hallmarks of cancer





Two enabling characteristics for acquiring hallmarks

Genome instability and mutation

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Tumor-promoting Inflammation

Hanahan & Weinberg (2011) Cell; Hanahan & Coussens (2012) Cancer Cell



Obesity, Physical Activity and Hallmarks of Cancer



Hanahan and Weinberg, Cell, 2011





Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective

Cancer Research Fund

American Institute for Cancer Research











SUMMARY OF STRONG EVIDENCE ON DIET, NUTRITION, PHYSICAL ACTIVITY AND PREVENTION OF CANCER

Convincing decreased risk Probable decreased risk Convincing increased risk Probable increased risk Substantial effect on risk unlikely	MOUTH, PHARYNX, LARYNX (2007)	NASOPHARYNX (2007)	DESOPHAGUS (2007)	LUNG (2007)	STOMACH (2007)	PANCREAS (2012)	GALLBLADDER (2015)	LIVER (2015)	COLORECTUM (2011)	BREAST PREMENOPAUSE (2010)	BREAST POSTMENOPAUSE (2010)	OVARY (2014)	ENDOMETRIUM (2013)	PROSTATE (2014)	KIDNEY (2015)	SKIN (2007)
Foods containing dietary fibre																
Aflatoxins																
Non-starchy vegetables ¹																
Allium vegetables									_							
Garlic			_	_												
Fruits ²																
Red meat																
Processed meat																
Cantonese-style salted fish									_							
Diets high in calcium ³																
Salt, salted and salty foods																
Glycaemic load																
Arsenic in drinking water																
Mate									_							
Alconolic drinks*						_					0					
Conee Data caratana5														-		
Beta-carotene-																
Physical activity"																
Adult attained haights									8		e e		2	-	2 2	
Greater hirth weight														27	29. 16	
Lactation										2						
Lastation																



- BREAST (MOTHER), OBESITY (CHILD)
- BREASTFEEDING
- MPL, OESOPHAGUS, STOMACH, COLORECTUM (DF), LUNG
- MPL, BREAST, COLORECTUM, LIVER, OESOPHAGUS PLANT FOODS (F&V, PULSES, WHOLEGRAINS)

NUTRITION AND CANCERS

- COLON, RECTUM, STOMACH (non-cardia) ALCOHOL
- COLON, BREAST, ENDOMETRIUM

- BREAST (PM), COLORECTUM, ENDOMETRIUM,

Research

ADIPOSITY

und International

OESOPHAGUS, PANCREAS, GALLBLADDER, KIDNEY, OVARY, PROSTATE (ADVANCED), LIVER

PHYSICAL (IN)ACTIVITY

MEAT – RED AND PROCESSED



NUTRITION AND CANCERS

- Causal factors
 - Some dietary components (alcohol, processed meat, carcinogens)
 - Unhealthy body composition (too fat, too thin)
 - Physical inactivity, sedentariness
- Protective factors
 - Healthy body composition
 - Physical activity
 - Healthy dietary pattern (eg Mediterranean, others)



RECOMMENDATIONS

BODY FATNESS

Be as lean as possible within the normal range of body weight

PHYSICAL ACTIVITY Be physically active as part of everyday life

FOODS AND DRINKS THAT PROMOTE WEIGHT GAIN Limit consumption of energy-dense foods Avoid sugary drinks

> PLANT FOODS Eat mostly foods of plant origin

ANIMAL FOODS Limit intake of red meat and avoid processed meat

> ALCOHOLIC DRINKS Limit alcoholic drinks

PRESERVATION, PROCESSING, PREPARATION

Limit consumption of salt Avoid mouldy cereals (grains) or pulses (legumes)

DIETARY SUPPLEMENTS

Aim to meet nutritional needs through diet alone

BREASTFEEDING

Mothers to breastfeed; children to be breastfed

CANCER SURVIVORS

Follow the recommendations for cancer prevention

The Panel emphasises the importance of not smoking and of avoiding exposure to tobacco smoke



Association between the WCRF/AICR score and total cancer risk



Cox regression model stratified by centre and age, and adjusted by energy intake, level of school, smoking status, presence of chronic diseases at baseline, ever use of contraceptive pills, ever use of HRT, age at first menarche, age at first pregnancy, and menopausal status

Romaguera D et al, AJCN 2012



Association between the WCRF/AICR score and total

mortality



Cox regression model stratified by centre and age, and adjusted by level of school, smoking status, smoke intensity, and menopausal status

Vergnaud AC et al, AJCN 2013



WCRF and ACS recommendations and cancer – systematic review

- Ten large prospective studies; 12 publications
- Strong and consistent evidence
- Greater adherence to score associated with lower overall cancer incidence and mortality
- Both men and women
- Also breast, colorectal, endometrium

Kohler LN et al, CEBP 2016, 25, 1-11

Number of deaths and age-specific mortality rates, all malignant neoplasms, by sex, UK, 2006





IMPACT OF OFFSPRING SIZE AND GROWTH ON CANCER RISK - 2007

Height and colorectal cancer; cohort studies





Height and cancer CUP 2015

Every 5 cm increment in height increases risk of cancers of:

- Kidney -10%
- Breast (pre-menopausal) 9%
- Breast (post-menopausal) -11%
- Ovary 8%
- Pancreas 7%
- Colorectum 5%
- Prostate 4%



Significant shifts in emphasis 1997-2007-CUP

- Adiposity and activity vs foods and drinks
- Lifecourse (height)
 - Overall nutritional/metabolic state (susceptibility)
- Foods vs nutrients
- Plant foods vs fruit and veg
- Whole diets vs individual foods
 - Markers of a pattern of diet and other behaviours (activity, smoking etc)



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The science and art of preventing disease, prolonging life and promoting health through organised efforts of society

Acheson Committee of Inquiry into the Future Development of the Public Health Function and Community Medicine, 1988.







All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.



Certainty (proof) is unattainable – degrees of uncertainty

Evidence accrues and conclusions may change

Is the evidence strong enough to take action?



Reasons for uncertainty

- Measurement error
 - Diet, activity, anthropometry (cf adiposity); cancer subtypes
 - Random error, systematic bias
- Study design
 - RCT vs cohort
 - Mechanistic
- Confounding
 - Smoking
 - Nutrient vs food
 - Multiple collinearity eg PA
- Exposure homogeneity
- Small effect size



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Eliminate choice: regulate to eliminate choice entirely.

Restrict choice: regulate to restrict the options available to people.

Guide choice through disincentives: use financial or other disincentives to influence people to not pursue certain activities.

Guide choice through incentives: use financial and other incentives to guide people to pursue certain activities.

Guide choice through changing the default: make 'healthier' choices the default option people,

Enable choice: enable people to change their behaviours.

Provide information: inform and educate people.

Do nothing or simply monitor the current situation.



Interventions - issues

- Strength of evidence
- Impact of intervention
- Side effects of intervention
- Cost
- Public and political acceptability







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Global variation in cancer incidence



Globocan, WHO



30 25 20 Breast 15



* Per 100,000, world population standard



Bottom Line

The key messages are robust

- Be active, and don't be sedentary and keep it up as long as possible
- Eat enough but not too much don't get too thin or fat
- Eat food not pills
- Mostly from plants, emphasise wholegrains and pulses
- Avoid highly processed energy dense foods and sugar sweetened beverages (and alcohol, processed meat and salty foods)
- Grow appropriately from conception to adulthood
- Get your mother to be well nourished before getting pregnant. And to breastfeed you.





If you already have a diagnosis of cancer, the evidence on nutrition and outcome is not strong, but the best advice is to follow (as far as possible) the recommendations for cancer prevention





The evidence is good enough to justify action

- Evidence for nutrition and cancer
- Evidence for effective interventions

Action needs leadership from government and health professionals



The WCRF/AICR Continuous Update Reports



Analysing research on cancer prevention and survival



http://www.wcrf.org/cancer_research/cup/key_findings/index.php







Watch this space....

2018 update is coming...



http://www.wcrf.org/cancer_research/cup/key_findings/index.php







Watch this space....

2018 update is coming...



May 2018

http://www.wcrf.org/cancer_research/cup/key_findings/index.php



Thank you!





Height and risk of CVD and cancer

World Cancer Research

MALES:

Fund International





Cancer & Nutrition NIHR infrastructure collaboration

Improving cancer prevention and care. For patients. For clinicians. For researchers

National Institute for Health Research

Cancer and Nutrition NIHR infrastructure collaboration

Improving cancer prevention and care. For patients. For Clinicians. For researchers.



Full Report of Phase One July 2015

Aim:

To help facilitate translational research in cancer and nutrition which will generate the evidence to improve cancer prevention and care

Objectives:

To bring coherence to existing activities by

- creating a framework for future research
- establishing better networks between cancer and nutrition stakeholders



Estimates of cancer preventability by appropriate diet, nutrition, physical activity and body fatness

	USA	UK	BRAZIL	CHINA
Mouth, pharynx, Iarynx	63	67	63	44
Oesophagus	63	71	50	33
Lung	36	33	36	38
Stomach	47	45	41	33
Pancreas	19	15	11	8
Gallbladder	21	16	10	6
Liver	30	24	13	7
Colorectum	50	47	41	22
Breast	33	38	22	11
Ovary	5	4	3	1
Endometrium	59	44	37	21
Prostate (advanced)	11	9	5	4
Kidney	24	19	13	8
Total for these cancers	31	32	25	24
Total for all cancers	21	24	18	20



Changes to conclusions for strong evidence since 2007



Analysing research on cancer prevention and survival

Cancer	Exposure	2007	New		
Colorectum	Dietary fibre	Prob ↓	Convincing ↓		
Endometrium	Coffee	-	Prob 🗸		
	Glycaemic load	-	Prob ↑		
Liver	Body fatness	LS ↑	Convincing ↑		
	Coffee	-	Prob ↓		
Kidney	Height	LNC	Prob ↑		
	Alcohol	Effect unlikely	Prob 🕇		
Bladder	Arsenic	LS 🕇	Prob ↑		
Ovary	Body fatness	LNC	Prob 1		
Pancreas	Folate	Prob ↓	LNC		
Prostate	Body fatness	LNC	Prob 🕇 (adv)		
	Height	LNC	Prob 1		
Oesophagus	Fruit/veg/βcarotene/vit C	Prob ↓	LS↓/LNC		
Stomach	Body fatness	LNC	Prob 🕇 (cardia)		
	Alcohol	LNC	Prob		
	Processed meat	LNC	Prob 1 (non-cardia)		
	Fruit/veg	Prob 🗸	LNC/LS		



Obesity and Cancer – Potential Mechanisms









DIET, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER SURVIVAL (BY TIMEFRAME)

	Timing of exposure assessment	BEFORE D	IAGNOSIS	LESS THAN AFTER DI	12 MONTHS AGNOSIS	12 MONTHS OR MORE AFTER DIAGNOSIS				
		DECREASES RISK	INCREASES RISK	DECREASES RISK	INCREASES RISK	DECREASES RISK	INCREASES RISK			
		Exposure Outcome	Exposure Outcome	Exposure Outcome	Exposure Outcome	Exposure Outcome	Exposure Outcome			
STRONG	Convincing									
EVIDENCE	Probable									
LIMITED EVIDENCE	Limited- suggestive	Physical All mortality BC mortality Foods containing fibre	Body fatnessAll mortality BC mortality2 2nd BCTotal fatAll mortalitySaturated fatty acidsAll mortality		Body All mortality fatness BC mortality ² 2nd BC	Physical activityAll mortalityFoods containing fibreAll mortalityFoods containing soyAll mortality	Body All mortality fatness			
	Limited-no conclusion ¹	Fruits, vegetables, foods of containing soy, carbohydra glycaemic load, protein, di alcoholic drinks, dietary pi body fatness (premenopatheight, energy intake	containing folate, foods ate, glycaemic index, etary supplements, atterns, underweight, use), adult attained	Foods containing fibre, ca fat, saturated fatty acids, activity, underweight, body adult attained height, ene	rbohydrate, protein, total alcoholic drinks, physical / fatness (premenopause), rgy intake	Fruits, vegetables, foods containing fibre, foods containing folate, foods containing soy,), carbohydrate, glycaemic index, glycaemic load, protein, total fat, saturated fatty acids, alcoholic drinks, dietary patterns, physical activity, body fatness, underweight, height, energy intake				
STRONG EVIDENCE	Substantial effect on risk unlikely									

All mortality, All cause mortality; BC mortality, breast cancer mortality; 2nd BC, Second primary breast cancer

STRONG: Evidence strong enough to support a judgement of a convincing or probable causal relationship and generally justify making recommendations

LIMITED: Evidence that is too limited to justify making specific recommendations

1 Includes various exposure-outcome combinations where evidence was available but too limited to draw conclusions. For more details of the outcomes related to the exposures listed here, see the full Breast Cancer Survivors SLR

2 Postmenopause only

DIET, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER SURVIVAL (BY OUTCOME)



STRONG: Evidence strong enough to support a judgement of a convincing or probable causal relationship and generally justify making recommendations LIMITED: Evidence that is too limited to justify making specific recommendations

1 Post menopause only

Continuous update Project Report: Diet, Nutrition, Physical Activity and Breast Cancer Survivors: <u>http://www.wcrf.org/sites/default/files/Breast-Cancer-Survivors-2014-Report.pdf</u>





Summary of Breast Cancer Survivors Report

Although there were significant associations between some exposures and outcomes, incomplete adjustment for potential confounders restricted the ability to ascribe causality

CUP Panel concluded that evidence is limited





* Per 100,000, world population standard





Factors that affect the risk of cancer: a conceptual framework



Behaviour

- People behave like those around them
 social norms
- Asking people to behave very differently from their social norm only has limited or unsustained effect
- Personal choice determines individual variation around the social norm
 - small effect
- External factors determine social norms
 - big effect