Diet, physical activity and cancer risk

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Abstract

There is a clear and consistent association between overweight and risk of hormone-related cancers, large bowel cancer and cancer at some other sites. Overweight is the consequence of an excess of energy intake over expenditure, but there is little evidence of an association between high energy intake and cancer risk in humans at any site other than the endometrium. This may be because of the difficulties in measuring total energy intake in the tens of thousands of individuals used in large prospective epidemiological studies. In contrast, despite the difficulties in measuring physical activity in the large numbers of persons needed in epidemiology, there is a growing body of evidence that a high level of recreational physical activity is protective against cancer at all sites associated with overweight.

Keywords
Diet
Overweight
Energy balance
Physical exercise
Recreational exercise
Occupational exercise
Cancer risk
Breast cancer
Colorectal cancer
Prostate cancer
Endometrial cancer

Key messages

- Overweight is a major risk factor for cancer at many sites, particularly for hormone-related cancers.
- There is no evidence for an association between cancer and excess energy intake.
- Good evidence exists for a protective effect of recreational exercise against cancer of the colon, breast and prostate—it is not known whether this is a direct effect or via having a lower body weight.

Introduction

There is wide acceptance that diet is a major risk factor for cancer at several sites in the human body. Poor diet and dietary deficiency is associated with cancer of the oesophagus, stomach and liver, whilst dietary excess is associated with the 'cancers of western civilisation' such as colorectal, breast, endometrial and prostate cancers[1]. Although physical activity influences many aspects of digestion, the main interaction of interest in cancer causation is with total energy intake and overweight.

Regular physical activity has been an important part of normal human lifestyle throughout evolution. Lack of physical activity was historically associated with power, or wealth, or both. It's usual corollary, overweight, was therefore a sign of success and a matter of pride. However, during the last 50 years there has been a steady decrease in physical activity in western populations. This has been through mechanization and automation both in the workplace and in the home, the widespread use of the car for even short journeys, the increased numbers of automatic doors, escalators and lifts, etc, all of which reduce the need for physical effort. Overweight is the natural consequence of an excess of energy intake over expenditure. In consequence, although according to FAO food intake data there has been a steady decrease in total energy intake in many EU countries during the last 15 years, there has been a steady increase in prevalence of obesity caused by the even more rapid decrease in energy expenditure. It is now commonplace to be obese. Further, it is now recognised that obesity, as well as being unsightly, is also unhealthy. It is no longer a matter of pride to be obese, but more a matter of concern.

To determine the effect of these recent changes in energy intake, exercise levels and overweight on cancer risk the main tool available to us is human epidemiology. This is an extremely blunt instrument, made even blunter by the difficulties experienced in measuring physical activity in populations. Of the three factors, weight is the easiest to measure, physical activity is the most difficult, and energy intake is intermediate.

Overweight and risk of cancer

'Overweight' is an intellectual concept that is subject to fashion. The nineteenth century beauties seen in portrait galleries were all, to our eyes, grossly overweight. More

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Table 1 Relative risk of cancer at various sites in obese persons (BMI >30 compared to 20–25)

Cancer site		ref 2*	ref 3	ref 4
Stomach –	male	1.88		1.10
	female	1.03		1.10
colorectum –	male	1.73		1.30
	female	1.22		1.20
Pancreas	male	1.62		
Prostate	male	1.29	2.5	1.90
Breast	female	1.53	1.6	1.20
Endometrium	female	5.42	6.4	2.00
Kidney	male	1.91		
	Female	2.03		2.00
Gallbladder	male			1.90
	Female			1.90

Data for those >140% of mean weight relative to mean weight.

recently, the symbol of female beauty of the 1950's, Marilyn Monroe, is now thought by modern youth to have been fat. She was not! But I accept that that is a matter of opinion. However, we are no longer simply concerned with images of beauty but with health risks, and so we need an objective measure of overweight.

The first major population study of overweight and cancer risk was the American Cancer Society One Million study[2]. This showed (Table 1) that 'overweight', defined as more than 30% above the average, is clearly associated with an excess risk of cancers of the colon and prostate in men, and of the colon, breast, endometrium, ovary and gallbladder in women. This was simply a study of weight as a percentage of the mean. Since the mean weight in the US is steadily increasing these data are not only difficult to interpret but are also difficult to use predictively. In 1988 La Vecchia *et al*[3] studied body mass index (BMI = weight/height squared), and obtained essentially similar results. In 1996 Moller *et al*[4] carried out a huge record linkage study on the whole Danish population, and again obtained results similar to those by the ACS and by La Vecchia *et al*.

In case-control studies BMI has usually been used as the measure of overweight, and this is one of the WHO standard measures[5]. The data from case-control studies relating overweight to cancer risk at specific sites have not been as consistent (Table 2) as those from the cohort studies. The UK Dept of Health COMA panel were unimpressed with the evidence[6] for an excess risk at sites other than for endometrial and post-menopausal breast cancer in women and perhaps male colon cancer. In the recent reports of the huge Italian case-control studies[7–8] there was clear evidence of a relation between overweight and risk of both breast cancer[7] and colorectal cancer[8]. The association with obesity is overwhelming for endometrial cancer and also for the relatively rare gallbladder cancer[2–4]. The BMI takes no account of fat distribution and there is evidence that for heart disease excess weight at the waist is a greater risk factor than that at the hips. In the field of heart disease there has therefore been interest in the waist to hip ratio as a superior measure of obesity than BMI. There is little information on waist to hip ratio as a risk factor for human cancer. However, since it takes no account of height, and since height appears to be a risk factor at least for post-menopausal breast cancer[9], it is likely that a measure of overweight that took this into account (such as BMI) might be expected to be a better indicator of cancer risk.

The next question is whether overweight is an independent risk factor for cancer *per se* or whether it is a surrogate measure of excess energy intake or lack of exercise.

Total energy intake and cancer

There is abundant evidence from animal studies that total energy intake is a major independent risk factor for cancer at all sites as well as at individual sites. The pioneering work of Tannenbaum[10] showed impressively

Table 2 Data on energy balance and obesity and cancer from the COMA report (6)

Relationship		Observation
Physical exercise		Outside of the scope of the report
Energy intake		No relationship to colorectal cancer or to breast cancer (pre- or post-menopausal) but increased risk of endometrial cancer with high energy intake
Overweight/obesity		
Breast cancer	Pre-menopausal	9/25 found increased risk 11/25 found decreased risk
	Post-menopausal	23/29 found increased risk 6/29 found lower risk
Colorectal cancer	Men	–4/7 case-control and 10/12 prospective studies showed increased risk
	Women	2/5 case control and 6/9 prospective studies showed increased risk
Prostate cancer	Case-control	3/8 show increased risk with overweight
	Prospective	5/8 show increased risk with overweight
Endometrial cancer		All case-control and all prospective studies showed increased risk with overweight

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that restriction of energy intake to rats and mice resulted in prolonged life and decreased cancer risk. Later studies by Tucker and Roe extended these results. Roe asked the question 'why is there an epidemic of cancers among laboratory animals?'[11]. They noted that modern laboratory animals were relatively free of infection, and so *ad libitum* feeding resulted in them being grossly overweight. They showed that meal patterns (*ad libitum* feeding compared with set meals) was an important risk factor, with those animals eating at set meal times being slimmer, more active, longer lived, and having much lower cancer risks than those with the same total energy intake but feeding *ad libitum*. Similarly Kritchevsky and his team[12] have shown greatly decreased colorectal cancer risk (and greatly prolonged life span) in animals fed with only 60% of the energy consumed by rats fed *ad libitum*. The case from the animal studies looks overwhelming.

It is disappointing therefore that a similar clarity of evidence is not seen in the studies of excess energy intake in humans. Indeed the COMA report[6] concluded that there was little evidence that excess energy intake was a risk factor for cancer at any site in the body. This could be for a number of reasons, all related to the essential differences between the animal model studies used and human epidemiology.

In the animal models, animals of a single genetic strain housed under standardised conditions are fed standardised diets in measured quantities. The animals have no choice of menu, and eat what they are fed. The composition of the diet is known, standardised, and reproducible. Human lifestyle is not like that. Humans are of mixed genetic composition and they eat varied meals that vary from person to person and from day to day and between seasons. The first problem is therefore the difficulty of measuring total energy intake against this background in the large populations needed in human epidemiological studies. Estimating food intake qualitatively is hard enough but quantitative measurement is very much harder. The lack of relationship between the measure of total energy intake and the cancer risk may therefore simply be resulting from the lack of precision of the diet estimates in human studies compared to the high level of precision in the animal studies. In other words, the animal studies are the more likely to give correct information.

However, the second difficulty is the nature of the animal models. Most rat strains do not get cancer, and so in order to be able to study the disease it is usual either to select high-risk strains or to use chemical carcinogens to initiate the cancer. Strains of rats with, for example, a high risk of breast cancer, may be more akin to humans with the BRCA-1 gene and are totally dissimilar to the sporadic breast cancers that account for more than 98% of the total. For this reason it is more usual to use models in which the animal is given a chemical cancer initiator at a level which gives half the animals the cancer of choice. Diet manipulation is then studied to see whether the proportion with cancer can be decreased (protection) or increased (promotion). The problem with this approach is that different initiators give different results with respect to diet[13] as illustrated in Table 3. We rarely know the nature of the initiator of human cancer and so we do not know which of the animal models (if any) is most relevant. Thus although there is a clear and strong association between excess energy intake and cancer risk in the animal models, it is possible that because the models are not necessarily good ones of the human disease there is no such relationship in humans.

For this reason, we cannot use the animal studies to help us to determine the relative importance of energy intake and energy consumption to overweight. We must instead concentrate our attention on the human data. There is no evidence for the strong relationship seen in the animal models, and the association with overweight is therefore presumably caused by overweight *per se* or to a lack of exercise.

Physical exercise and cancer risk

Although it is very difficult to measure total energy intake accurately, it is even more difficult to measure energy expenditure in epidemiological studies involving tens of thousands of subjects. An early attempt[14] to get markers of exercise was used in the study of heart disease in British civil servants. As all of them had an extremely sedentary occupation their only exercise was either recreational or during their journey to and from the office. If their daily journey entailed at least 20 minutes walking, this was associated with only 50% of the risk of heart disease seen in the non-walkers. Recreational walking (with the dog, for example) was equally protective if done on a daily basis. Similarly if they had a garden and spent more than a certain time per week cultivating it then again this reduced the risk of heart disease to 50% compared to those with no garden. In contrast, 'explosive' sport such as squash gave no protection.

Table 3 Fiber and colorectal cancer in animal models (data from ref. 10)

Fibre source	Observation
Pectin	Promotion, protection or no effect depending on the initiator used, on it's route of administration, and on the sex of the animal
Hemicellulose	Result depended on the route of administration of the initiator
Cellulose	Result depended on the type and route of administration of initiator
Wheat bran	Protection in male but not female Fischer rats, and if the initiator Is given orally but not subcutaneously.

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Table 4 The relationship between physical exercise and cancer risk in the Norwegian prospective study of Thune *et al.* (12–14)

Cancer site		Effect of increased physical activity
Prostate cancer		Occupational—non-significant decrease Recreational—decreased risk of cancer
Testicular cancer		No effect of exercise on risk
Colon	Female	Occupational—no effect Recreational—protective, particularly for proximal colon
	Male	Occupational—protective Recreational—protective, particularly for proximal colon
Rectum		
	Female	No effect of exercise
	Male	No effect of exercise
Lung		
	Female	No effect of exercise on risk
	Male	Protection by recreational but not occupational exercise Effect is on adenocarcinoma and small cell carcinoma but not on squamous cell carcinoma.
Breast		Recreational and occupational activity protective. Effect is greater for pre- than for post-menopausal, and greater in younger than older women.

There were similar attempts to obtain markers of sustained exercise and 'explosive' exercise in studies of cancer risk. These have been described in the excellent studies of Thune *et al.*[15–17]. Again it was sustained exercise, both occupational and recreational, that was most protective. The results are summarised in Table 4. Clearly, in cancers of the breast, large bowel and prostate, all of which are associated with overweight, there is also an association with lack of exercise.

There is, in fact, a considerable body of evidence of a role for exercise in cancer prevention, and this was recently reviewed by Moore *et al.*[18]. The strength of the evidence suggests that increasing the level of physical exercise might have an important effect on cancer risks. If we make the very reasonable assumption that the level of occupational exercise is not going to increase, the aim must be to increase the level of recreational exercise. People need to be persuaded that increasing their level of recreational exercise will not only help them to control their weight but will also give them considerable health benefits.

Conclusions

There is evidence that overweight and lack of physical exercise are important risk factors for cancers at a number of sites in the body. We need better measures of overweight and of exercise in order to be more confident about the observations. We could then begin the complex task of unravelling the inter-relationships between these two sets of variables. We could also hope to begin to understand the mechanisms behind the observations. However we do not need to await a full understanding before utilizing the results of empirical observation. Edward Jenner was vaccinating people with cowpox virus to prevent smallpox long before we had even isolated any virus. It was more than a century before we began to understand the relationship between cowpox and smallpox. I doubt if, even now, we fully understand exactly how smallpox infection kills.

In fact, most European countries have programmes for stimulating recreational exercise. These should be supported by all of us working in the field of cancer prevention in particular, and promotion of good health in general. We have few enough good ideas for cancer prevention as soundly based as this. Apart from the anti-smoking campaigns, promotion of recreational exercise is the strategy most likely to be successful in preventing cancers at a number of sites including the breast, colon and prostate—sites where cancers are most common in western populations.

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