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COMMENTARY

Chemical carcinogens and overnutrition in diet-related cancer

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The intake of known dietary carcinogens was compiled and the cancer risk was estimated on the basis of carcinogenic potencies in animals as derived from the Carcinogenic Potency Database by Gold and co-workers. The total cancer risk was compared with the number of cancer cases attributed by epidemiologists to dietary factors (one-third of all cancer cases, i.e. ~80 000 per one million lives). Except for alcohol, the known dietary carcinogens could not account for more than a few hundred cancer cases. This was seen both with the DNA-reactive carcinogens (heterocyclic aromatic amines, polycyclic aromatic hydrocarbons, *N*-nitroso compounds, estragole, aflatoxin B_1, ethyl carbamate, to name the most important factors) as well as with those carcinogens which have not been shown to react with DNA (e.g. caffeic acid and the carcinogenic metals arsenic and cadmium). Residues and contaminants turned out to be negligible. Among the various possibilities to explain the discrepancy we investigated the role of overnutrition. Dietary restriction in animals is well known for its strong reducing effect on spontaneous tumor formation. These data can be used to derive a carcinogenic potency for excess macronutrients: the tumor incidence seen with the restricted animals is taken as a control value and the increased tumor incidence in the animals fed *ad libitum* is attributed to the additional feed intake. For excess standard diet in rats, a carcinogenic potency TD_{50} of 16 g/kg/day was deduced from a recent study. Overnutrition in Switzerland, estimated to be 5.5 kcal/kg/day, was converted to excess food (1.9 g/kg/day) and the cancer incidence was calculated. The result, 60 000 cancer cases per one million lives, is provocatively close to the number of cases not explained by the known dietary chemical carcinogens. Mechanistic studies will be required to test our hypothesis and investigate the role of different types of macronutrients in overnutrition.

Introduction

Doll and Peto (1), in their review on 'Quantitative estimates of avoidable risks of cancer' stated that 'it may be possible to reduce US cancer death rates by practicable dietary means by as much as 35%'. This figure resulted from a 90% reduction of deaths from stomach and large bowel cancer and a 50% reduction of cancer of the endometrium, gallbladder, pancreas and breast. However, the degree of uncertainty in this estimate was expected to be large, so that values between 10 and 70% were considered possible. The authors also indicated that 'there is still no precise and reliable evidence as to exactly what dietary changes would be of major importance'. Ten years later, Doll (2) reviewed his conclusions and stated that 'the estimate that the risk of fatal cancer might be reducible by dietary modification by 35 percent remains a reasonable guess'.

Ames *et al.* (3) ranked carcinogenic hazards on the basis of human exposure estimates multiplied by the carcinogenic potency in rodents. They concluded that dietary carcinogenic hazards from current levels of pesticide residues or water pollution are likely to be of minimal concern relative to the background levels of natural substances. The importance of the natural carcinogens could not be estimated in absolute terms because the authors itemized highly specific exposure situations which could not be summed and compared with the results of epidemiological predictions. Perera and Boffetta (4) also pointed out that the results were influenced by the selection of chemicals which was dictated by the nature and availability of both exposure and rodent potency data.

In this paper, we attempt to estimate the cancer risk in Switzerland associated with the intake of known dietary carcinogens on the basis of estimates of average dose and carcinogenic potency, and we address the question of whether the total dietary cancer risk equals the number of cases attributed by epidemiologists to dietary factors. With cancer being the cause of death in about one-quarter of the population in Switzerland, and with the assumption that one-third of this is due to diet-related factors, about one-twelfth of all deaths should be attributable (80 000/10^6 lives).

Methods

Exposure estimates

Our approach is based on average daily intake estimates for dietary carcinogens in Switzerland, mainly from the Swiss Nutrition Report (5) and from a special issue of *Mutation Research*, edited by Aeschbacher (6). Specific references are given in Tables I and II. Differences in exposure due to specific dietary habits are mentioned in well-documented situations (e.g. ethyl carbamate and arsenic).

For the class of dibenzodioxins and dibenzofurans, exposure was expressed in 2,3,7,8-tetrachlorodibenzo(*p*)dioxin (TCDD*) equivalents. For the class of polynuclear aromatic hydrocarbons (PAH), a similar approach described by Kramers and van der Heijden (7) was used with benzo[*a*]pyrene equivalents: B[*a*]P levels in the food were multiplied by a factor of 15, in order to account for the other PAHs.

Carcinogenic potency estimates

Carcinogenic potencies TD_{50} were derived from the four issues of the Carcinogenic Potency Database by Gold *et al.* (8–11). TD_{50} values approximate the daily carcinogen dose per kg body weight which halves the probability of remaining tumorless within a standard lifespan (2 years in the database). From each study (defined by the study number), the lowest significant ($P < 0.05$) TD_{50} value was used. When more than one study fulfilled our criteria, the

*Abbreviations: TCDD, 2,3,7,8-tetrachlorodibenzo(*p*)dioxin; PAH, polynuclear aromatic hydrocarbons; B[*a*]P, benzo[*a*]pyrene; TD_{50}, dose rate that halves the lifetime probability to stay tumor-free (2 years for rodents); IQ, 2-amino-3-methylimidazo[4,5-*f*]quinoline; MeIQ, 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline; Glu-P-1, 2-amino-6-methyldipyrido[1,2-*a*:3′,2′-*d*]imidazole; Glu-P-2, 2-aminopyrido[1,2-*a*:3′,2′-*d*]imidazole; Trp-P-1, 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole; Trp-P-2,3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole; AαC, 2-amino-9*H*-pyrido[2,3-*b*]indole; MeAαC, 2-amino-3-methyl-9H-pyrido-[2,3-*b*]indole; NOC, *N*-nitroso compounds; NDMA, *N*-nitrosodimethylamine; NPYR, N-nitrosopyrrolidine; PCDD, polychlorinated dibenzodioxins; PCDF, polychlorinated dibenzofurans; DEHP, bis(2,2′-diethylhexyl)phthalate; CPDB, Carcinogenic Potency Database.

Table I. Risk estimate for dietary carcinogens shown to form DNA adducts, based on daily intake and carcinogenic potency (TD_{50} values; daily dose resulting in 50% lifetime tumor incidence). Risk estimates (cancer cases per 10^6 lives) are rounded off to one-digit numbers

Compound or class	Average human intake estimate for Switzerland (ng/kg body wt/day)	TD_{50} geometric mean (no. of studies) (mg/kg body wt/day)	Estimated cancer cases per 10^6 lives	Ref. for human intake estimate	Ref. for carcinogenic potency in animals
Heterocyclic aromatic amines	1500	15 (26)	50	5	8,9,10,11
Polycyclic aromatic hydrocarbons	200 ($B[a]P_{equivalents}$)	3 (3)	30	5,7	8,9,10
Nitroso compounds, volatile (NDMA, NPYR)	14	1 (20)	8	32,13	8,9,10,11
Estragole	1000	50 (1)	10	33	10
Aflatoxin B_1	0.25	0.02 (16)	6	34	8,10
Ethyl carbamate basal intake	20	30 (14)	0.3	35,36	8
+ wine drinking	100	30 (14)	2	35,36	8
+ spirit drinking	2000	30 (14)	30	35,36	8
Benzene	100	70 (9)	0.7	15	8,10,11
Trichloroethylene	50	1000 (10)	0.03	37	8,10,11
1,1,1-Trichlorethane	50	500 (2)	0.05	38	8
Vinyl chloride	3	60 (32)	0.03	5	8,9,11
Styrene	10	600 (2)	0.008	5	8

Table II. Risk estimate for dietary carcinogens which have not been shown to form DNA adducts, based on daily intake and carcinogenic potency (TD_{50} values; daily dose resulting in 50% lifetime tumor incidence). Risk estimates (cancer cases per 10^6 lives) are rounded off to one-digit numbers

Compound or class	Average human intake estimate for Switzerland (ng/kg body wt/day)	TD_{50} geometric mean (no. of studies) (mg/kg body wt/day)	Estimated cancer cases per 10^6 lives	Ref. for human intake estimate	Ref. for carcinogenic potency in animals
Ethyl alcohol (ethanol)			8000[a]		
Caffeic acid	10^6	> 400 (1)	< 1000	18	39
Arsenic					
basal intake	150[b]	> 0.2[c]	< 400	5	
+ fish	500[b]	> 0.2[c]	< 1000	5	
Cadmium (chloride)	200	> 1.3 (1)	< 80	5	8
TCDD	0.002 ($TCDD_{equivalents}$)	0.00007 (7)	10	5	8
Zearalenone	100	30 (2)	2	40	9
Ochratoxin A	2	11 (2)	0.09	41	11
Estradiol	2[d]	1 (1)	1	42,43	8
DEHP	2000	1000 (4)	1	5,44	8
Tetrachloroethylene	50	110 (5)	0.2	45	8,10
Dieldrin	15	2 (16)	4	5	8
DDT	30 (incl. isomers)	30 (23)	0.5	5	8,10
$\alpha + \beta$ Hexachlorocyclohexane	30	20 (3)	0.8	5	8
Captan	20	1100 (4)	0.009	5	8
Saccharin (sodium salt)	500 000	>>2000 (4)	<< 100	46	8,10

[a]Substantially less in non-smokers (1).
[b]Includes organic As (carcinogenicity proven for inorganic As only).
[c]From epidemiological data (12).
[d]From meat (endogenous production/physiological concentration).

geometric mean was calculated. The number of studies used is given in parentheses in Tables I and II. The TD_{50} value for tumor-bearing animals was always used when this was the lowest value in a significant study.

Using 1,1,1-trichloroethane as an example, study no. 2735 (female rats) by Gold *et al.* (8) showed a TD_{50} entry of 226 mg/kg/day with $P < 0.0005$ for tumor-bearing animals. The respective value for study no. 2736 (male rats) was 950 mg/kg/day with $P < 0.009$. The geometric mean (463 mg/kg/day) was rounded off to a one-digit score. A TD_{50} value of 500 mg/kg/day is given in Table I.

The class mean for the heterocyclic amines included 2-amino-3-methylimidazo [4,5-*f*]quinoline (IQ), 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ), 1-amino-6-methyldipyrido[1,2-*a*:3',2'-*d*]imidazole (Glu-P-1), 2-aminopyrido[1,2-*a*:3',2'-*d*]imidazole (Glu-P-2), 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-1), 3-amino-1-methyl-1-methyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-2), 2-amino-9*H*-pyrido[2,3-*b*]indole (AαC), and 2-amino-3-methyl-9H-pyrido-[2,3-*b*]indole (MeAαC). For the volatile *N*-nitroso compounds (NOC), nitrosodimethylamine and nitrosopyrrolidine were used. For the PAH, the carcinogenic potency of B[*a*]P was used (see section on exposure estimates for explanation of equivalent dose).

Epidemiological data were used for alcohol (1) and for arsenic (12) because animal models were considered inappropriate for these two carcinogens.

Risk = dose × potency

For the risk estimations, the following assumptions were made: (i) the cancer risk is approximated by the mathematical product of dose rate × potency; and, (ii) the carcinogenic potency is assumed to be independent of the dose rate, i.e. a linear dose–response relationship is assumed. This might be correct for the DNA-reactive carcinogens listed in Table I but is most likely too conservative for the non-DNA-reactive carcinogens of Table II. With mechanistic information supporting a non-linear dose–response relationship, a '<' sign is therefore introduced in the respective column. This is not done with risks which are already negligible with linear extrapolation.

The units used are ng/kg body wt/day for the dose and mg/kg body wt/day for the carcinogenic potency TD_{50}. The risk is expressed as cases per million persons exposed for life (cases per 10^6 lives). No distinction is made between incidence and mortality.

Example (see also Table I). The average daily intake of ethyl carbamate (urethane) for humans who do not consume alcoholic beverages is 20 ng/kg body wt/day. The carcinogenic potency (TD_{50}) is 30 mg/kg body wt/day. Therefore, the daily dose is 1.5 million times lower than the dose that results in a 50% cancer incidence (500 000 cases/10^6 lives). The cancer risk from ethyl carbamate in Switzerland for people who drink no alcoholic beverages therefore is 500 000:1 500 000 ~ 0.3 in 10^6 lives.

Carcinogens included in the evaluation

This study does not inlcude all (suspected) carcinogens ever detected in the diet. Our quantitative analysis deals primarily with the well-known classes of genotoxic carcinogens and with those individual carcinogens that are either potent or are ingested in high amounts. For carcinogens only taken up in trace amounts, our analysis is confined to one or two representatives. If the risk associated with the model compound turns out to be negligible, similar situations are not further evaluated. Unusual dietary habits are not evaluated (e.g. pyrrolizidine alkaloids in special herbal teas).

We did not include in our evaluation all natural carcinogens listed by Ames *et al.* (13). For some carcinogens, the carcinogenicity studies could not be evaluated (e.g. psoralenes: require light; the hydrazine agaritine in the common mushroom: artificial dosing regimen), others are ingested only in minute amounts (such as constituents of spices). A number of natural carcinogens are taken up with vegetables or fruits. For this situation, it is difficult to quantitate the carcinogenic potency because the cancer-protective nature of the food items could more than compensate for the carcinogenic effect of some of their constituents.

Endogenous formation of carcinogens

Some carcinogens are not only of dietary origin but are also produced endogenously. This is true, e.g. for formaldehyde. The endogenous contribution is not taken into account in the following analysis because the respective cancer cases would not belong to the 35% related to dietary carcinogens. This percentage was deduced from comparing various populations that showed different dietary habits and cancer mortality rates (1). Under the assumption that endogenous formation of carcinogens does not vary between populations to the same extent as dietary intake, cancer due to endogenous factors would have to be counted with the remaining, not diet-related, 65% cancer cases.

Results

DNA adduct-forming carcinogens

Table I lists a number of dietary carcinogens that have been shown to bind covalently to DNA. The first column gives an estimate for the exposure situation, the second column shows the carcinogenic potency in animal tests and the third column combines the two values and represents the cancer risk expressed as the number of expected cases per 10^6 lives. Reference is given to both the intake estimate and the carcinogenic potency.

Intermediate risk factors. Risk factors of up to 50 cancer cases per 10^6 lives are derived from heterocyclic aromatic amines (e.g. as pyrolysis products) and from the PAH. NOC rank somewhat lower. In the latter class, only the volatile representatives have been included because the data on non-volatile NOC were sparse both for exposure levels and carcinogenic potency. To provide a rough estimate, Shephard (14) indicated that the non-volatile NOC could become as important as the volatile ones. The formation of these three classes in the diet is strongly dependent on the temperature. Therefore, reducing the frying or broiling temperature could result in some reduction of the cancer risk.

A number of natural constituents in a variety of food items have been shown to be carcinogenic (13). Among the DNA-reactive carcinogens, estragole appears to be top ranking, mainly because of its relatively high intake (e.g. in the volatile oils of some vegetables such as fennel). Caution must be expressed here, however, not to take this risk at face value because of the protective aspects associated with the intake of vegetables.

The cancer risk estimated for the fungal toxin aflatoxin B_1 was at 6 per 10^6 lives. The exposure to fungal toxins is highly variable and depends upon individual nutritional habits. Frequent consumption of peanuts or figs could increase the exposure to aflatoxins.

Low risk factors. For ethyl carbamate (urethane), the risk level is largely dependent on the consumption of alcoholic beverages. While for people who do not drink alcohol, the risk level is negligible, wine drinkers are in a low risk situation and regular consumption of stone-fruit brandies can represent an intermediate risk.

Contamination of food with benzene is thought to be primarily the result of a general contamination of the air. On this basis, exposure by inhalation will be more important than through the diet (15).

Negligible risk factors. Many categories that produce headlines in the media are responsible only for a negligible dietary cancer risk. This is true for environmental contaminants (chlorinated compounds), for substances that migrate from packaging material into the food (vinyl chloride or styrene) or for residues of veterinary drugs (dimetridazol; data not shown).

Questionable risk factors. Formaldehyde is not listed in Table I. Firstly, the endogenous production from demethylation reactions (primarily in cholesterol biosynthesis) is about two orders of magnitude larger than the dietary exposure (estimated to be ~70 μg/kg/day; 16). Secondly, a carcinogenic effect of formaldehyde was seen only at dose levels that were highly cytotoxic for the nasal epithelium. The tumor incidence increased with the 4th power of the dose. The respective potency values cannot, therefore, be used for low dose levels.

Dietary carcinogens without proven DNA adduct formation

A large number of dietary constituents increase the tumor incidence in animal experiments but have not been shown to be genotoxic by interaction with DNA. These carcinogens are listed in Table II. Their mechanisms of action could be indirect genotoxicity, e.g. via increased production of oxygen radicals, or epigenetic carcinogenicity, e.g. via sustained stimulation of stem cell division. It is also possible that some compounds attributed to Table II do actually form DNA adducts and should therefore belong to Table I. More mechanistic information will be required to classify these carcinogens correctly.

Again, average human exposure levels and carcinogenic potencies are compiled. The cancer risk was estimated on the basis of the same assumptions made for the mutagenic carcinogens. It must be noted for this group, however, that a linear dose–response extrapolation from high (often toxic) dose levels in the bioassay is most probably too conservative (17). This also means that the risk values shown in column 3 of Table II are probably overestimated whenever the dose extrapolation from the TD_{50} values to the human exposure levels has to cover many orders of magnitude.

Top risk factors. In this group, the highest ranking known dietary carcinogen is ethanol. Epidemiologists attribute 3 (2–4) % of all cancer deaths in the USA to alcohol (1). This is equivalent to ~8000 cases per 10^6 lives. Beause of a multiplicative

synergism with smoking the number of cancer cases contributed by alcohol alone would be smaller but still the highest in absolute terms.

High risk factors. The next highest risk factors are derived from natural dietary constituents and metals. The polyphenol caffeic acid is one of 27 dietary components reported to be carcinogenic among 52 'natural pesticides' tested in high-dose animal cancer tests (13). Caffeic acid is present in a large number of food items and is also formed from chlorogenic acid and neochlorogenic acid which show highest concentrations in roasted coffee beans. With an estimated average human exposure level on the order of 1 mg/kg/day even the low carcinogenic potency of a TD_{50} of 400 mg/kg/day would result in an appreciable number of induced cancer cases (on the order of $1000/10^6$ lives). A problem associated with this figure is the fact that polyphenols are also known as anti-carcinogens when combined with genotoxic carcinogens (18). It is possible, therefore, that the risk at human exposure levels will be much lower or even non-existent.

Arsenic and cadmium also rank highly. The 3-fold span for the risk from arsenic is due to individual dietary habits with respect to the consumption of fish. The carcinogenic potency of arsenic was derived from epidemiological data on inorganic arsenic in drinking water in Taiwan (12): a TD_{50} value has been calculated for 40–59 year old persons, where a total dose of 10 g arsenic resulted in a 2% excess morbidity in skin cancer. The risk values given in Table II probably represent upper limits because arsenic compounds in fish are largely organic and much less toxic than the inorganic species. Furthermore, the dose–response relationship is unlikely to be linear for metal ion-induced carcinogenicity.

The data available for cadmium are based on one single bioassay with cadmium chloride. Its relevance for dietary Cd is questionable.

Theoretically, a risk value of 100 would be derived for saccharin, on the basis of an average intake of 0.5 mg/kg/day and a carcinogenic potency of the sodium salt of TD_{50} = 2000 mg/kg/day. However, we list saccharin at the bottom of Table II because the mechanism of carcinogen action in the rat bladder is based on factors which do not appear to operate in humans (19).

Intermediate risk factors. It is difficult to comment on the risk derived for polychlorinated dibenzodioxins (PCDD) and polychlorinated dibenzofurans (PCDF) (in TCDD equivalents; 10 cases/10^6 lives): on the one hand, a non-linear dose–response relationship would result in a lower risk, on the other hand, the longer half life of TCDD in humans as compared with rodents would result in higher tissue levels at comparable exposure levels.

Low and negligible risk factors. The fungal toxins zearalenone and ochratoxin A from contaminated foods represent cancer risks of 2 and lower (per 10^6 lives). Natural levels of estradiol in meat, or plasticizer bis(2,2′-diethylhexyl)phthalate (DEHP) migrating from packaging materials into foods represent negligible risks. The risk associated with chlorinated compounds from persistent environmental contamination by pesticides are also negligible. This is in agreement with the analysis presented by Ames *et al.* (13), and is in strong contrast to the public concern about this class of compounds. It nicely illustrates the gap between toxicological risk assessment and risk perception (15).

Summary for the known dietary carcinogens

The risk values calculated for individual carcinogens (or classes of carcinogens) span about one million-fold and most are extremely low. For the class of the DNA adduct-forming carcinogens (Table I), only ~100 cancer cases per 10^6 lives can be explained. For those carcinogens which have not been shown to form DNA adducts (Table II) only ethanol can clearly be attributed a sizeable fraction of the diet-related cancer cases.

Discussion

Our analysis shows that the exposure of humans to the known dietary carcinogens is unlikely to explain the cancer cases attributed by epidemiologists to dietary factors. The discrepancy could be explained by a number of reasons. A first explanation could be that humans are more sensitive than rodents, i.e. that the carcinogenic potencies used in our analysis are underestimated when using the Carcinogenic Potency Database (CPDB). Within this context, two different aspects have to be considered, (i) the species extrapolation and, (ii) different exposure periods in the animal bioassay versus the situation with dietary factors in human carcinogenesis. In a bioassay, the treatment normally starts when the animals are 6–8 weeks old. Humans, on the other hand, are already exposed to diet-related carcinogens *in utero* and during childhood.

For those carcinogens where both animal data and epidemiological evidence are available, the potencies expressed per kg body weight per day for seven out of eight carcinogens fall within one order of magnitude (20). It is therefore unlikely that the reasons listed above could be responsible for a general underestimation of the carcinogenic potency in humans.

Another possibility and, in our view, a more likely explanation of the above mentioned discrepancy is the idea that we have missed the most important dietary carcinogens. We do not think that this is true for the DNA adduct-forming carcinogens. The extensive short-term testing for mutagens in the diet would have picked up important DNA-reactive carcinogens.

It is interesting to note that the most important known carcinogen (alcohol) actually is of low potency but is ingested in large amounts. An organism has to adapt to handle gram amounts of a compound. This might entail responses that could alter the process of spontaneous carcinogenesis. On the other hand, for substances where the human intake is low (up to a few milligrams per person per day) an adaptive response is normally not induced and no effect of the substance on endogenous carcinogenesis is expected (unless the compound has hormone-like activity, such as TCDD).

The question therefore arises whether compounds eaten in gram amounts (the macronutrients fat, carbohydrates, protein or salts) have to be regarded as the most important 'carcinogens'. Epidemiological studies have indeed shown an association between overnutrition and the occurrence of cancer at several sites, for instance in the breast, large bowel, and prostate. The following quantitative analysis of dietary restriction experiments provides surprising results in terms of a carcinogenic activity of excess macronutrient intake.

Overnutrition as a dietary 'carcinogen' for animals

Carcinogenic potency of excess macronutrients. In animals, it has been known for 50 years that dietary restriction results in a dramatic reduction of spontaneous and chemically induced cancer incidence (see reviews 21, 22). Such data could be used to derive a 'carcinogenic potency' for excess macronutrients: the tumor incidence seen with the restricted animals can be taken as a control value and the increased tumor incidence in the animals fed *ad libitum* is attributed to the additional feed intake. As an example (23), one group of 50 female DBA mice was fed with

only 2 g of a mixture of dog chow meal and skimmed milk powder per mouse per day. Not a single breast tumor developed within 20 months. Another group received, in addition, corn starch *ad libitum*. Average daily feed consumption was 2.9–3.1 g, i.e. they consumed 1 g of corn starch in addition to the 2 g basic feed. In this group, the 'spontaneous' breast cancer incidence was 38%.

These data can be interpreted as if the additional 1 g carbohydrate/day for a 30 g mouse (i.e. 33 g/kg/day) was carcinogenic for the breast (38% increase). Expressed in terms of a TD_{50} value, the 'carcinogenic potency' of overnutrition by corn starch for the mouse mammary gland, adjusted to 24 months (8), therefore could be estimated to be $33:38 \times 50 \times 0.69 =$ 30 g/kg per day. Similar analyses could be made for other macronutrients. For instance, fat in the form of 'Kremit' (24) could be attributed a TD_{50} value of 3 g/kg/day.

For our analysis of the 'carcinogenic potency' of overnutrition we focus on a much more recent study performed with 1200 rats (the Biosure study, 25, 26; final data kindly provided by the authors as a personal communication). Untreated groups of rats fed *ad libitum* and kept for up to 30 months showed a crude malignant tumor incidence of 36 and 37%, for males and females respectively. Groups kept at 80% of that feed intake showed only 13 and 19% malignant tumors. The difference of 23 and 18% for males and females was highly significant. It is based on crude incidence rates and does not even take into account that many tumors observed in the restricted animals only showed up when most of the *ad libitum* mice had died. Organs that showed a significant difference in 'amount of feed-related' tumor incidence were the endocrine pancreas, the pituitary gland, the mammary gland, the lung and mesenteric lymph nodes.

Based on average body weights of 541 g for the males and 330 g for the females (at an age of 18 months) and on the difference in feed intake of 3.2 and 2.9 g per day (for males and females respectively), carcinogenic potencies TD_{50} for excess regular feed of 11 and 20 g/kg/day, for male and female rats, can be calculated (for males: $3.2{:}0.541{:}\ (36-13) \times (100-13){:}2 = 11.2$; no correction to standard lifespan). This carcinogenic potency is between the values derived for corn starch and fat in the mouse. It indicates that rats and mice could react in a quantitatively similar manner to excess food and gives us hope that extrapolation to humans might not be completely unrealistic.

The data do not allow the distinction between the risk of tumor development from excess energy, carbohydrate, fat or protein. Analysis of the various animal experiments might give some information, but only mechanistic investigations will allow the biology of spontaneous carcinogenesis and the role of different types of macronutrients to be understood.

Overnutrition and human cancer

Average caloric intake in Switzerland in 1985–1987 (excluding alcohol) was 2315 kcal/person/day (5). Basal requirements (8 h each lying, sitting, and standing, for the age group 20–39) are at 1963 kcal/person/day (27). Therefore, the average Swiss is overfed by ~5.5 kcal/kg/day. If this caloric overnutrition is converted to rat maintenance diet on the basis of 3 kcal metabolizable energy per gram, an excess of 1.9 g food/kg body wt/day can be calculated. If we further assume humans to be as sensitive as rats to the 'carcinogenicity' of overnutrition (TD_{50} of 16 g/kg/day as an average of male and female rats) we can speculate that 60 000 cancer cases per 10^6 lives could be attributable to excess food intake in Switzerland. This value is provocatively close to the number of cancer cases not explained by the known dietary chemical carcinogens.

Mechanistic aspects

Energy is essential for life and minimum requirements must be met both for the basal metabolism and for physical activity. It is the high-level excess in laboratory rodents fed *ad libitum* for which we have derived a 'carcinogenic potency'. The TD_{50} value most probably depends both on the level of overnutrition and on the nature of the food eaten in excess. A small excess cannot be attributed the same 'carcinogenic potency' as gross overnutrition.

Epidemiological data show some correlation between obesity and certain types of cancer (1) but the relationship is not as strong as would be expected on the basis of our analysis. The discrepancy might be due to the fact that not all individuals in a heterogeneous human population show the same relationship between overcaloric nutrition and obesity.

Another question is whether the data can be explained in a biologically plausible manner. The process of carcinogenesis is considered to be dependent on the level of DNA damage and the rate of DNA synthesis that is required to fix the primary DNA lesions in the form of heritable mutations (28). Overnutrition could have an effect on both aspects. It could increase the rate of oxidative DNA damage believed to be a major factor in ageing and cancer (29) and it could result in a higher rate of cell turnover.

These hypotheses are supported by the finding that caloric restriction has a more pronounced beneficial effect on the late phase than on the early phase of carcinogenesis, if an initiation–promotion protocol is used (30). Also, dietary restriction in mice beginning at one year of age still had a significant beneficial effect on survival times and spontaneous tumor incidence (31). Such an instantaneous effect is compatible with the idea that tumor progression was retarded, for instance by a reduced rate of cell division in the clones of initiated cells. In view of dietary recommendations, the available data, therefore, indicate that it is never too late to gain from avoiding overnutrition.

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Note to readers

The authors do not consider the lists presented in this paper to be final. Readers are welcome to contribute new or missing data on exposures and carcinogenic potency, and to call our attention to other data which may pertain.

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