Risiken erkennen – Gesundheit schützen

Study on meat intake and mortality

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In March of this year the daily press discussed an American study on the relationship between the consumption of red meat and an elevated mortality rate caused by diseases such as cancer and cardiovascular disorders. The Federal Institute for Risk Assessment (BfR) evaluated the article by Sinha et al. "Meat Intake and Mortality" and the evidence for a relationship between an increased mortality rate and increased meat consumption.

The prospective cohort study examined whether the consumption of red meat (beef, pork), white meat (poultry, fish) and sausage products (cold cuts, ham, sausages) led to elevated mortality from cancer, cardiovascular diseases and other causes of death. To this end, the data on meat consumption and the causes of death from around 550,000 men and women aged 50 to 71 years from six US States and two cities were collected over a period of 10 years. The cohort was divided into five groups according to the amount of meat consumed. In the study, consumers with the highest intake of red meat and sausage products were found to have a 31% (men) and 36% (women) higher mortality rate than people in the group with the lowest consumption. In the case of white meat the reverse effect was observed, i.e. increased consumption of poultry and fish correlated with a decreased mortality risk over the examined time period.

According to the BfR, the prospective study is suitable for statistical evaluation of the data. Furthermore, an adequate amount of individuals were studied in order to warrant a representative result.

However, no direct causal relationship between meat consumption and cancer and other causes of death can be established from the Sinha study. There are several conceivable causes that could lead to increased mortality from the consumption of red meat: chemical compounds formed during the preparation of meat, genetic factors, dietary habits and lifestyles of the respondents, iron content of meat, the intake of unsaturated fatty acids from other foods, the amount of fruit and vegetables consumed and the possible hormone residues in meat. When evaluating the data, the study authors therefore took into account variables such as family history with cancer, smoking, sport, fruit and vegetable consumption which can also influence the study outcome. The authors indicate that additional confounding factors, which could not be considered, can lead to distortion.

It is yet to be determined whether the results can be transferred to consumers in Germany due to differing consumer habits and possible differences in meat production and preparation. Since meat also contains valuable amino acids, useful iron and B vitamins, it remains an important food for a healthy and balanced diet. According to the results of the Sinha study, poultry and fish even lower the mortality risk in the examined time period.

1 Subject of the assessment

In March a study by the authors Sinha et al. entitled “Meat intake and mortality: a prospective study of over half a million people” was published in *Arch Intern Med.* 2009 Mar 23;169(6):562-71 (Sinha study). The study examined whether a relationship exists between the intake of so-called red meat (especially beef and pork), white meat (especially poultry and fish) as well as processed meat and elevated mortality resulting from cancer, cardiovascular diseases, accidents and other causes of death (e.g. infectious diseases, diabetes, etc.) for individuals aged 50-71 years. The authors of the study came to the conclusion that the

elevated intake of red or processed meat – in comparison of groups with high and low meat intake – is associated with a moderately elevated rate of total deaths as well as deaths caused by cancer, cardiovascular diseases in men and women. The examination of the intake of white meat revealed the opposite trend.

2 Results

Overall, the following conclusions were drawn from the research data in this study:

1. Besides the general problems associated with the collection of food consumption data, the Sinha study cannot be criticised methodologically. The evidence of this study on a relationship between red and processed meat intake and elevated mortality – especially through cancer – is in line with numerous empirical studies from different countries including the USA, Japan, Finland, Norway, Sweden and others. These studies also identified a statistically significant relationship between high intake amounts of red meat and cancer, especially colorectal cancer. This relationship has also been verified by a number of meta-analyses.

2. A causal relationship between meat intake and cancer as well as other causes of death cannot clearly be deduced from the data presented in this study. The occurrence of cancer is a multifactorial process involving genetical as well as other factors, which were not considered in all of the studies. The occurrence of cancer can also be connected with chemical compounds that are generated e.g. during food preparation. In some of the studies, the authors noted genetic risk factors involved in the development of cancer in relation to the intake of read meat. In principle, a confounding effect is possible. This effect could arise due to the correlation of other cancer-promoting eating habits or lifestyles with meat intake. Although the study results are adjusted for a number of confounding variable, additional confounding effects cannot be ruled out, as the authors also indicate. As a result of an unadjusted confounding variable, the examined risk factor is often overestimated.

3. It is known that potentially carcinogenic compounds such as heterocyclic amines and polycyclic aromatic hydrocarbons can occur during meat preparation. The BfR discusses this in its Frequently Asked Questions about barbecues (BfR FAQ, 21 June 2007). Nitrates, nitrites and *N*-nitroso compounds, which also appear in meat, are considered to be precursors of or candidates for carcinogenic substances. Consumers should be informed that a different type of preparation can effectively reduce the development of compounds dangerous to their health. Additional factors that may play a role include the meat's iron content, saturated fats in the meat and the length of time it remains in the intestines, the amount of fruits and vegetables consumed for the USA, the amount of hormone residues in meat are also factors. Furthermore, increased amounts of cooking salt during the intake of read meat and from products processed from red meat such as certain sausage products may play a role.

4. The depicted effects of meat intake are usually calculated for the consumer category "highest intake" compared with "lowest intake". In the cited study of Sinha, the US-American study population was divided into five groups (quintiles) according to intake amount. A slightly elevated risk was found in nearly all intake groups in comparison with the "lowest intake" group, and this effect was especially visible in comparison with the "highest intake" group. The intake data of the Sinha study refer to total energy intake, which complicates the comparison with absolute intake amounts. With this restriction, the intake amounts of surveyed Americans seem similar to the intake data of the average

German in the EPIC study (EPIC=European Prospective Investigation into Cancer and Nutrition). A direct comparison is still problematic in both countries due to different eating habits, potentially different meat production and preparation, different survey methods of intake data and potentially different frequencies of manners of death. Thus, the results of the Sinha study can be only be transferred with a high degree of uncertainty. The complete transferability of data to Germany remains to be resolved.

3 Reasons

The statistical evidence for the relationship between the intake of red meat and the occurrence of cancer based on the above mentioned article by Sinha was assessed. Additionally, meat intake data from Germany and the USA were compared with regard to the study and a summary of the evidence from additional studies including meta-analyses is presented.

3.1 Statistical evidence from the study by Sinha et al., 2009

The aim of the Sinha study was to examine the effect of red, white and processed meat intake with regard to the risk for the total or specific mortality in a cohort study of Americans aged 50-71. A cohort study is a prospective type of epidemiological study in which the health of study participants is examined over a longer period of time. This method is better suited for this research question than e.g. case-control studies since the latter allow no retrospective collection of the exact intake habits (exposure) especially for the case group (deaths). From an epidemiological point of view, cohort studies are considered as having more statistical weight in the study of a potential risk factor. The cohort examined comprised individuals aged 50-71 years old who were registered in the AARP (American Association of Retired Persons). Data on meat intake as well as cause of death were collected for a total of 322,263 men and 223,390 women from 6 US states (California, Florida, Louisiana, New Jersey, North Carolina and Pennsylvania) and 2 cities (Atlanta and Detroit) over a period of 10 years (1995-2005).

Intake amounts and habits were determined through questionnaires (124 questions on food intake and on consumption over the last 12 months) and verified by two 24-hour recalls.

The types of consumed meat were defined as follows:

- Red meat: beef and pork (beef, pork, venison and the meat of small ruminants is commonly referred to as “red meat” in English use)
- White meat: chicken, turkey, fish
- Processed meat: ham, beef or pork sausage, chicken sausage, luncheon meats (red and white meat), cold cuts (red and white meat), cooked ham, hot dogs/sausages

The types of causes of death were divided into:

- Cancer (all types)
- Cardiovascular diseases
- Accidents and sudden death
- Other causes of death such as tuberculosis, diabetes, AIDS, infectious and parasitic diseases, Alzheimer’s disease, septicemia, pneumonia, influenza, liver diseases etc. and unknown causes of death

3.1.1 Statistical methods in the Sinha study

Cox Proportional Hazard Regression was used to examine the relationship of mortality rates (number of deaths per period of time) and risk factors. This method is the first choice for prospective (cohort) studies. Based on the amount of meat intake, five groups were established

of which the group with the lowest meat intake (first quintile of intake data) served as reference group.

Age, education, marital status (married: yes/no) family history with cancer (yes/no; only mortality through cancer), ethnic group, body mass index, smoker (subdivided into 31 categories), exercise, energy intake, alcohol consumption, vitamin intake, fruit consumption, vegetable consumption, menopausal hormone therapy for women were used as controlled variables for the adjustment of potential confounding. The results of the study were statistically adjusted according to this for the known or suspected confounding factors.

3.1.2 On the presentation of results of the Sinha study

47,976 deaths in men and 23,276 deaths in women were registered over the 10-year course of the study. Men and women in the quintile with the highest meat intake had a moderately but significantly increased mortality risk compared with the lowest quintile. A so-called hazard rate (HR) of 1.31 for men and an HR of 1.36 for women was determined. This can be interpreted as a 31% (men) or 36% (women) higher mortality rate regarding the reference group in the time period examined. For the specific deaths, cancer mortality was elevated in the quintile with the highest intake (men HR 1.22 and women HR 1.2), cardiovascular disease mortality was also elevated (men HR 1.27 and women HR 1.5) as well as other causes of death.

In men, a relatively high intake of red meat correlated with an increased mortality probability caused by injury/accidents and sudden death.

Processed meat showed an increased risk for all causes of death in total (men HR 1.16 and women HR 1.25), for cancer death (men HR 1.09 and women HR 1.38) or cardiovascular diseases and other causes of death, but not for accidents and sudden deaths.

The opposite effect was observed for white meat; i.e. women and men who ate more white meat had a lower mortality rate in regard to total deaths (men and women HR 0.92), cancer deaths and deaths categorised as “other deaths”.

On a whole, the intake of red and processed meat was associated with a moderate increase in the total mortality rate, the cancer and cardiovascular disease mortality rate as well as other causes of death with the exception of accidents/injuries and sudden deaths.

If men and women in the studied age group (50-71) would reduce their intake amounts of red meat to that of the group with the lowest intake, then the mortality risk is expected to be reduced by 11% in men and 16% in women over the observed period of time. The portion of cardiovascular disease mortality of total mortality could be reduced by 11% for men and 21% for women. By reducing the intake of processed meat, the cardiovascular disease mortality for women over the period of study of 10 years could be reduced to 20%.

3.1.3 Assessment of method and results

A prospective cohort study – as it was used in the Sinha study – is appropriate for this type of study since the participants can be observed over a longer period of time, allowing the study of the difference of exposed and unexposed individuals with regard to mortality rate. The methods used for the statistical evaluation of data are appropriate for the research question. The study was comprehensive with a sufficient number of persons included.

The limitations that occur in most food consumption studies such as determining eating habits retrospectively through questionnaires, which could result in uncertainty concerning the actual amounts eaten, could also apply to this study, even if researchers attempted to verify information through 24-hour recalls. A confounding effect is in principle possible. For example, it could be based on a correlation of meat intake with other eating or lifestyle habits that promote the cause of death. Although the study results have been adjusted for a number of confounding factors, additional confounding effects cannot be ruled out as indicated by the authors. As a result of an unadjusted confounding factor, the risk factor studied is usually overestimated.

The intake data of the Sinha study refers to the total daily energy intake which complicates the comparison with absolute intake amounts. Intake data from Germany/ Europe and USA are compared under Point 2 (3.2) Comparison of intake data from Germany/Europe and the USA

The evidence of this study on a relationship between the intake of red and processed meat and an increased mortality rate especially through cancer is in line with a number of empirical studies from different countries including the USA, Japan, Finland, Norway, Sweden and others. These studies also found a statistically significant relationship between high intake of red meat and cancer, especially colorectal cancer. Since then, this relationship has been verified through a number of meta-analyses, as depicted in point 3 (3.3.).

However, the existing data do not allow the definite deduction of a definitive causal relationship between meat intake and cancer as well as other causes of death. It is highly likely that the causes for the relationship between increased mortality rate and increased intake of red and processed meat are multifactorial. In addition, genetic and other factors that were not considered in all studies could play a role. The occurrence of cancer could also be related to chemical compounds which develop, e.g. during food preparation. It is known that potentially carcinogenic compounds such as heterocyclic amines and polycyclic aromatic hydrocarbons can develop during food preparation. Nitrates, nitrites and *N*-nitroso compounds, which also occur in meat, are considered to be precursors of or candidates for carcinogenic substances. Iron in meat can raise the oxidative damage and lead to the development of *N*-nitroso compounds. Furthermore, meat can be a source of saturated fats, which are related to the risk of cancer. Growth stimulants approved in the USA for cattle farming (growth hormones or substances with hormone-like effects) could also play a role. Individuals who consume less red and processed meat and more fruits and vegetables as well as fish, have the possibility to ingest more substances from the latter foods, which may affect their health positively. In addition, the length of time that meat remains in the intestines could be a factor for increased risk of cancer. Furthermore, it was shown that genetic factors influence the development of cancer in relation to the intake of red meat.

The Sinha study cannot be criticised, aside from the general problems associated with the collection of food consumption data, on methodological grounds.

3.2 Comparison of intake data from Germany/Europe and the USA

Comparable intake data for Germany/Europe and the USA are difficult to obtain, in part due to methodological problems in data collection. The data depicted here are meant to provide a dimension to have an idea for a possible comparison.

The intake data from the Sinha study (table 1) allow no direct comparison and provide no direct daily intake amounts because they were calculated to gram per 1000 kcal.
A standard energy intake must be assumed in order to deduce a daily intake amount. This is illustrated for red meat in two examples each for women (with a 1700 and 2200 kcal requirement per day) and men (with a 1900 and 2600 kcal requirement per day). The indicated energy intake applies to a sedentary activity (life style).

Table 1: Intake data from the Sinha study

Daily intake determined for participants in the Sinha et al. 2009 study					
Men					
	1st quintile	2nd quintile	3rd quintile	4th quintile	5th quintile
Red meat intake (g/1000kcal)	9.3	21.4	31.5	43.1	68.1
* 1900 kcal/d → g/d	17.7	40.7	59.9	81.9	129.4
* 2600 kcal/d → g/d	24.2	55.6	81.9	112.1	177.1
Women					
	1st quintile	2nd quintile	3rd quintile	4th quintile	5th quintile
Red meat intake (g/1000kcal)	9.1	21.2	31.2	42.8	65.9
* 1700 kcal/d → g/d	15.5	36.0	53.0	72.8	112.0
* 2200 kcal/d → g/d	20.0	46.6	68.6	94.2	145.0

3.2.1 Meat intake in Germany

The intake data calculated for the USA can be compared with the following intake data from Germany (table 2)[1].

Table 2: Data on meat intake in Germany 1994-98

Mean (SD) daily intake (g/d)							
Total meat		Red meat		Poultry		Processed meat	
Men	Women	Men	Women	Men	Women	Men	Women
155.8 (124.1)	86.6 (81.4)	51.7 (87.7)	29.6 (56.6)	17.0 (55.9)	13.1 (42.1)	84.7 (89.9)	42.5 (55.7)

The average intake of red meat for men in Germany thus lies between the 2nd and 3rd quintile of the US data and that of women between the 1st and 2nd quintile of the US data.

According to the USDA (United States Department of Agriculture), the average intake of red meat in the USA in 2007 was 137.45 grams per day (retail weight)[2].

[1] Source: Gonzalez et al., 2006 (Food intake survey by 24-h recall during the recruitment phase from August 1994 to September 1998)
[2] Source: http://www.ers.usda.gov/Data/FoodConsumption/FoodGuideIndex.htm#meat

The intake data from the Sinha study refer to the total daily energy intake, which makes a comparison with absolute daily intake more difficult. With these limitations, the intake amounts of studied Americans seem similar to the intake data of the average German in the EPIC study. However, a direct comparison is problematic due to different eating habits, potentially different meat production and preparation, differences in intake data collection as well as potentially different frequencies of causes of death in both countries. The results of the Sinha study can thus only be transferred with a high degree of uncertainty. The complete transferability of the results to Germany remains to be clarified.

3.3 Summary of the evidence for a relationship between the intake of red meat and the risk of cancer from additional studies including meta-analyses

The level of the statistical evidence depends on the type of study. Meta-analyses (MA), which are based on a systematic review of literature, are generally attributed with the highest level of evidence. Prospective (cohort) study are especially well suited for this question. Thus, MA of independent cohort studies have the highest level of evidence. The following table also contains an MA that uses case cohort studies ending in kidney cancer (Faramawi et al., 2006). This study is listed for the sake of completeness. However, due to the type of study and the cancer disease examined in the study, is considered to have less weight. The meta-analyses listed sometimes use the same primary studies. The evidence from each meta-analysis study can thus not be considered independent from the others. The temporal gradation as well as the fact that all studies find a relationship, clearly indicates definitive cumulative evidence for a relationship. This also supports the idea that the overall finding is resistant to methodological differences between individual MA studies.

Table 3 depicts all known meta-analyses for the research question at hand concerning red meat intake and cancer risk. The MA studies indicate a relationship between high intake of red meat and an elevated risk for colorectal cancer.

Conclusions from the meta-analyses

- The studies consistently indicate a possible relationship between an increased intake of red meat and cancer (especially colorectal cancer).

Potential problems of assessment through meta-analyses on this subject

- Observational studies are subject to a possible confounding effect.
  - e.g. members of the group with the “highest intake” could have eating habits and lifestyles that lead to above-average exposure to carcinogens independent of meat intake.
- Definition of exposure
  - Meat, red meat, processed meat, processing procedure, intake amount in g/day: individual primary studies used different methods of data collection and sometimes different definitions in these areas.
- Definition of the disease
  - The case definition “colorectal cancer” is subject to a misclassification mistake, especially for wrong negative diagnoses. However, the effect would apply to the entire cohort regardless of the extent of meat intake and should thus be disregarded.
- Publication bias

- Studies with a positive association may be more likely to be published than studies with a negative association or with a statistically insignificant result. This can cause the effect to be distorted towards a high risk.

Table 3: Collection of known meta-analyses on the intake of red meat and human cancer risk

Year	Study	Population	Cancer	Results	Reference
2006	MA of 15 prospective studies (red meat, n=7.367) 14 prospective studies on processed meat (n=7.903)	Worldwide	Colorectal	Relative risk 1.28 (95% CI=1.15-1.42) for red meat and 1.20 (1.11-1.31) for processed meat	Larsson and Wolk 2006
2006	13 case-control studies	1966 and 2006	Kidney cancer	20% to 22% elevated risk for kidney cancer of those in the group with the highest intake level vs. those in the group with the lowest intake level of poultry and processed meat. 27% and 30% elevated risk for red meat.	Faramawi et al. 2006
2001	13 prospective studies	Studies until June 1999 USA, Norway, the Netherlands, Japan, Finland	Colorectal	Per 100g daily meat intake (total and red meat) significant risk increase of 12-17%. Per 25g daily meat intake (processed meat) significant risk increase of 49%.	Sandhu and White 2001
2002	Red meat: 9 prospective studies and 14 case-control studies Processed meat: 7 prospective studies and 16 case-control studies	Studies published 1973 to 1999 worldwide	Colorectal	Relative risk 1.35 (CI: 1.21-1.51) for red meat and 1.31 (CI: 1.13-1.51) processed meat for those in the group with the highest intake level vs. those in the group with the lowest intake level (highest vs. lowest quintile)	Norat et al., 2002
2006	Processed meat: 6 prospective studies and 9 case-control studies	Studies published 1966 to 2006 worldwide	Stomach cancer	Relative risk 1.15 (CI: 1.04-1.27) for prospective studies and 1.38 (95% CI 1.19-1.60) for case-control studies for an increased intake of 30g/day (half of the average intake amount) processed meat	Larsson et al., 2006
2007	Processed meat: 16 (12 could be evaluated) prospective studies and 71 (were not evaluated) Case-control studies Processed meat: 14 (5 could be evaluated) prospective studies and 44 (were not evaluated) case-control studies	Search frame is not indicated; studies published from 1975 to 2005 are included	Colorectal	Relative risk 1.43 (CI: 1.05-1.94) for intake amount/week and 1.29 (CI: 1.04-1.6) per 100g/day for red meat. Relative risk 1.21 (CI: 1.04-1.42) per 50g/day processed meat. The evidence for elevated risk of colorectal cancer was assessed as “convincing” by the reporting “panel”.	The World Cancer Research Fund/American institute for Cancer Research Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective Washington, DC, AICR; 2007

4 Scope for action / measures

Nutritional recommendations should have a balanced regard for the potential health risk as well as the potential health benefits. As a result of the studies at hand, the mortality rate for low intake of red and processed meat is reduced compared with that of the quintile with the highest intake. Meat contains valuable amino acids, is a good source of iron and B vitamins that can compensate a deficiency of these nutrients. In the Sinha study, white meat was even associated with a decrease in mortality rate of 50 to 71-year-olds over the examined period of time.

5 References

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