

*Invited review*

## Diet and colorectal cancer risk: current views

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### SUMMARY

Large bowel cancer (CRC) is amongst the most common cancers in North America, Australasia and western Europe. The major risk factors of CRC are genetic and dietary. Evidence regarding genetic polymorphisms which may influence the metabolism of nutrients thought to be important in the aetiology of CRC and colorectal adenomatous polyps is discussed. At present, the strongest evidence of gene-nutrient interaction in relation to CRC is for folate and genetic variants associated with differences in metabolism of folate. Significant trends of increasing CRC risk with increasing intake emerged for total energy, bread and pasta, cakes and desserts, and refined sugar have been observed in recent Italian studies. Most vegetables, including pulses, were inversely associated with CRC. Among macronutrients, a high intake of starch and saturated fat seemed to lead to an increased risk of cancer. High intakes of polyunsaturated fatty acids (chiefly derived from olive oil and seed oils) showed a marginal inverse association with CRC. In the present paper the relation between meat consumption and cancer risk is reviewed showing that there is little evidence to support this relationship.

**Key words:** cancer risk, colorectal cancer, diet, energy intake, genetic polymorphism, prevention, physical activity

Moreover, while weight excess is associated with increased CRC risk, physical exercise is inversely correlated to colon cancer.

Large bowel cancer is amongst the most common cancers in North America, Australasia and western Europe. Within Europe, the highest mortality levels among both men and women are found in the eastern and north-western countries, and the lowest levels in the south. Men and women show similar incidence/mortality rates for colon cancer, although men have much higher rates for rectal cancer.<sup>1</sup>

Within the UK, where the colorectum is ranked second for males and third for female sites of cancer mortality, the lowest rates are in the south of England (Oxford, South Thames and South West regions) and the highest in the North and east of Scotland and in the West Midlands.<sup>2</sup> There is only a slight socio-economic gradient for colorectal cancer and, in the UK, very little urban-rural difference although elsewhere in Europe the disease tends to be more common in urban areas.<sup>2</sup>

In Italy the incidence is higher in the northern regions as compared to the south and truly mediterranean area of the Country. Each year 27,000 new cases of colorectal cancer are diagnosed in Italy and 18,000 deaths for this cancer are observed.

### Genetic risk factors

Familial risk factors are known to play an important role in colorectal cancer (CRC) risk, particularly when the relatives are affected by early-onset cancer. Part of this familial aggregation can be accounted for by inherited forms of colorectal cancer, i.e. familial adenomatous polyposis (less than 1% of all CRC) and hereditary nonpolyposis colorectal cancer (about 3%). Other genetic factors may be involved in the development of adenoma or in the transformation of adenoma into carcinoma. That the existence of polymorphisms of the ade-

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nomatous polyposis coli gene increase susceptibility to both adenomas and cancer favours this hypothesis.<sup>3</sup> Interactions between environmental factors, and most of all dietary factors, and polymorphisms of carcinogen-metabolizing enzymes may also be involved. Better knowledge of these mechanisms will substantially widen the scope of colorectal cancer prevention.

Evidence regarding genetic polymorphisms which may influence the metabolism of nutrients thought to be important in the aetiology of colorectal cancer and colorectal adenomatous polyps was reviewed in occasion of a recent ECP consensus forming workshop.<sup>4</sup> At present, the strongest evidence of gene-nutrient interaction in relation to colorectal cancer is for folate and genetic variants associated with differences in metabolism of folate.<sup>5</sup> There is a need to clarify the relationship between cancer of the rectum and both folate intake and the *MTHFR* C6777T polymorphism. In addition, there is a need to identify the possible role of other genetic polymorphisms affecting folate metabolism, and the mechanisms underlying the apparent interaction between intake of folate and related nutrients and the genes influencing folate metabolism.<sup>5</sup>

A number of studies has been published on the possible relationship between colorectal neoplasia and the method of cooking meat and fish, and on polymorphisms that may affect the metabolism of carcinogens formed in cooking.<sup>6</sup>

There have been relatively few studies of cooking methods and colorectal neoplasia, and a crucial limitation is that exposure assessment is poor. The possibility of incorporating heterocyclic amine-adduct assays was raised, and it was suggested that they might potentially provide an integrate measure reflecting the balance between external exposure, endogenous activation and detoxification. In regard to the studies of potentially relevant polymorphisms, notably of the *GST*, *NAT* and *CYP* families, it was noted that both gene-environment and gene-gene interaction had been little studied, yet a priori it was most likely that these genes would exert effects only in the context of interaction.<sup>4</sup>

Moreover, somatic changes of genes in the WNT/wingless pathway, *K-ras*, *TGFb* and *p53* were considered as molecular markers of the heterogeneity in colorectal adenomas and cancers<sup>7</sup>. Two groups of colorectal cancer could be identified: LOH+ accounting for 880%, and MSI+ for 15%. Molecular changes in relation to adenomas, aberrant crypt foci and flat colorectal neoplasia are less clear. There is discussion of the possible logistical

impact of including such molecular characterization of tumours in a study of gene-nutrient interaction.<sup>4</sup>

### ***Diet is a major risk factor***

The major risk factor in colorectal carcinogenesis that has excited most interest is diet. Higginson, using the lowest incidence found in any population as representing that due to unavoidable factors, estimated that more than 90% of colorectal cancers could potentially be prevented, principally by the choice of the "right" diet.<sup>8</sup>

The epidemiology of the relation between diet and colorectal cancer has been racked by controversy, but has been reviewed some years ago by Boutron et al<sup>9</sup> and by Hill and Caygill.<sup>10</sup> Early population studies showed a strong correlation with dietary fat, particularly animal fat, but this was not born out by the case-control studies and so was widely rejected. Later case-control studies, particularly those from North America, have tended to support weakly a role for fat, and the study by Jain and co-workers showed a statistically significant correlation with a dose-reponse relation.<sup>11</sup> The prospective study of Willett et al has swung the argument back again; they showed a strong causal effect of meat/animal fat, a non-significant effect of vegetable fat and a protective effect of fish consumption.<sup>12</sup> These results agree very strongly with results from Caygill and Hill, who also showed that the strongest protective effect occurred when fish oil contributed a proportion of total animal fat, and that there was no protective effect when the animal fat intake was low.<sup>13</sup>

A major problem with the interpretation of the dietary fat data is the unfortunate way that the components have been grouped. For example, meat fat (causal?) and fish fat (protective?) are classified together as animal fat, olive oil (protective?) is classified together with other vegetable oils (neutral?) in vegetable fats and *n-3* polyunsaturated fatty acid-PUFA (protective?) and *n-6* PUFA (neutral?) are classified together as PUFA. This may be the cause of much of the confusion in the epidemiological literature.

### ***Italian studies on diet and colorectal cancer***

Between 1992 and 1996, 1953 subjects with cancer of the colon-rectum (median age: 62 years) and 4154 hospital controls were interviewed in six Italian areas.<sup>14-20</sup> The validated food-frequency questionnaire included questions on 78 foods and recipes, and specific questions on individual fat intake pattern.

Significant trends of increasing colorectal cancer risk with increasing intake emerged for bread and pasta, cakes

and desserts, and refined sugar<sup>14,15</sup> (Table 1). In Italy, white flour products end-up being a source of empty calories, which can lead to reduced intake of some beneficial micronutrients. They are also responsible for a high total energy intake and, because their glycemic index is very close to that of refined sugar, may facilitate high glucose and insulin levels and insulin resistance with promotion of cell growth.

Most vegetables, including pulses, were inversely associated with cancer of the colon and rectum.<sup>16</sup> High fruit intake was associated only with a reduction of rectal cancer. Total energy intake was directly associated with colorectal cancer risk<sup>14</sup> (Table 2). Among macronutrients, a high intake of starch and saturated fat seemed to lead to an increased risk of cancer<sup>17</sup> (Table 3). High intakes of polyunsaturated fatty acids (chiefly derived from olive oil and seed oils) showed a marginal inverse association with colorectal cancer risk. Among micronutrients, beta-carotene, vitamin E and calcium showed the most consistent inverse associations.<sup>18</sup> An excess of energy intake, particularly from refined bread and pasta, can be an unfavourable feature of the Mediterranean diet with respect to colorectal cancer risk, especially in the presence of sedentary life.

**Table 1.** Odds ratios (ORs) and corresponding 95% confidence intervals (CI) of cancers of the colon-rectum in the highest vs the lowest quintile of major food groups - Italy, 1991-1996 (Data from Franceschi et al; ref. 15).

COLON-RECTUM	Ors in highest vs lowest quintile	(95% CI)
Milk	0.83	(0.68-1.01)
Coffee and tea	0.79	(0.64-0.98)
Bread and cereal dishes	1.69	(1.36-2.10)
Eggs	0.92	(0.75-1.14)
Poultry	1.26	(1.00-1.57)
Red meat	1.14	(0.93-1.39)
Pork and processed meats	1.02	(0.84-1.24)
Fish	0.72	(0.59-0.88)
Cheese	0.99	(0.82-1.19)
Raw vegetables	0.59	(0.48-0.71)
Cooked vegetables	0.57	(0.47-0.69)
Potatoes	1.20	(0.96-1.51)
Citrus fruit	1.02	(0.85-1.22)
Other fruit	0.72	(0.60-0.87)
Cakes and desserts	1.13	(0.93-1.37)
Refined sugar	1.43	(1.19-1.73)

**Table 2.** Odds ratios (ORs) and corresponding 95% confidence intervals (CI) of cancers of the colon-rectum according to energy intake - Italy, 1991-1996 (Data from Franceschi et al; ref. 14).

COLON-RECTUM		
Quintile of energy intake	ORs	(95% CI)
1	1	
2	1.10	(0.92-1.31)
3	1.18	(0.99-1.42)
4	1.16	(0.97-1.39)
5	1.50	(1.25-1.80)
Continuous (100 kcal/day)	1.02	(1.01-1.03)

**Table 3.** Odds ratio (ORs) and corresponding 95% confidence intervals (CI) of cancers of the colon-rectum for a difference of 100 kcal/day in the intake of major macronutrients - Italy, 1991-1996 (Data from Franceschi et al; ref. 17).

COLON-RECTUM		
Macronutrients	ORs	(95% CI)
Protein	0.86	(0.77-0.97)
Sugar	0.99	(0.95-1.04)
Starch	1.10	(1.07-1.13)
Monounsaturated fat	1.00	(0.91-1.10)
Saturated fat	1.12	(0.98-1.28)
Polyunsaturated fat	0.89	(0.76-1.03)
Alcohol	1.01	(0.98-1.03)

An innovative approach was used by Calza et al to define a low-risk diet for colorectal cancer from the Italian multicentric case-control study.<sup>19</sup>

A logistic regression model was fitted on the reported intake of five macronutrients, and the estimated coefficients were used to compute a diet-related logistic risk score (LRS). The mean of LRS within risk decile ranged from 0.89 to 1.86. Total energy intake and absolute consumption of each macronutrient increased with increasing LRS. In relative terms, however, starch intake showed an almost threefold increase across subsequent score levels, while a decline was observed for unsaturated fat, sugar and protein. Saturated fat consumption remained fairly stable in relative terms. When food groups were considered, bread and cereals dishes, cakes and desserts and refined sugar were positively associated, while the consumption of vegetables, fruit, fish, poultry and olive oil was inversely associated with LRS.

## Olive oil

In the mediterranean basin, olive oil, along with fruits, vegetables, and fish, is an important constituent of the diet, and is considered a major factor in preserving a healthy and relatively disease-free population. Epidemiological data show that the consumption of olive oil, a fundamental constituent of the Mediterranean diet, has significant protective effects against colorectal cancer.<sup>20,21</sup> Recent data show that it is the unique profile of the phenolic fraction, along with high intakes of squalene of the extra-vergin olive oil which could confer its preventive effect on colorectal cancer.<sup>22-25</sup> The major phenolic compounds identified and quantified in olive oil belong to three different classes: simple phenols (hydroxytyrosol, tyrosol); secoiridoids (oleuropein, the aglycone of ligstroside, and their respective decarboxylated dialdehyde derivatives); and the lignans [(+)-1-acetoxypinoresinol and (+)-pinoresinol].<sup>22-25</sup> All three classes have potent antioxidant properties. High consumption of extra-vergin olive oils, which are particularly rich in these phenolic antioxidants (as well as squalene and oleic acid), should afford considerable protection against cancer (colon, breast, skin), coronary heart disease, and ageing by inhibiting oxidative stress.

## Fruit and vegetables

The evidence for a protective effect of fruit and vegetables has come from reviews of case-control studies<sup>26</sup> and the dose-response data from the North Italian study.<sup>27,28</sup> The evidence is generally accepted, and currently many European countries have campaigns to promote the consumption of fruits and vegetables. There is little evidence of their success. It is apparent that the socio-economic group with most need to increase their plant food consumption regard the risk of cancer in their old age as low on their list of priorities. The questions that always arise when trying to promote consumption of fruit and vegetables are:<sup>29</sup>

- How much should we eat? Currently the target (which varies between countries) is 500-600 g per day, but the epidemiological evidence suggests that the ultimate target is 800 g per day. This is based on data such as those from the North Italian study.<sup>28</sup> From such data La Vecchia and Tavani deduced that each extra portion of fruit or vegetables per day decreases the risk of cancer by 10%.<sup>28</sup>
- Which are best? All fruits and vegetables seem to be protective,<sup>30</sup> and there is no particular fruit or vegetable that is clearly "better" than the others. This is because all fruits and vegetables contain a wide array

of potentially protective substances, all of which seem to interact with each other. We do not know which particular components or classes of components are most important; for this reason we cannot say that any particular vegetable is better than any other. Not only do they all seem to be similarly protective, but also the best protection comes when you eat as wide a variety as possible.<sup>28</sup> A way to achieve this is to eat those that are in season and follow the natural cycles of supply.

- What if I don't like a particular vegetable? Not only do all fruits and vegetables contain a wide array of protective agents, but also all of the classes of protective agents are found in an array of different fruit/vegetables. In consequence, if you do not like a particular vegetable (e.g. broccoli) there is nothing in it that cannot be found in alternative vegetables, at least one of which is likely to be palatable. You should therefore eat the ones that you enjoy and leave the ones that you don't like on one side.
- How do I achieve the target? The target of 500 g per day is readily achievable. The target of 800 g is more difficult but can be achieved by, for example, having a glass of fruit juice with your breakfast (one), having salad with your midday and evening meals (two and three), eating „second vegetables“ (four and five), eating fruit between meals (six and seven) or after meals (eight and nine) etc.
- Will, for example, vitamin supplements do instead? Because all the antioxidants and anticarcinogens interact with each other synergistically none of them alone gives as much protection as does the same amount in a fruit or vegetables. So the recommendation is to eat fruits and vegetables! However, there are people who do not like these foods or who cannot eat a lot of this foods (i.e. patients with irritable bowel syndrome associated with diarrhoea). For them, vitamin supplements are better than nothing.

## Fibres

In the last two years there were two papers in the New England Journal of Medicine<sup>31,32</sup> which cast some doubt on the previous evidence that fibres play a preventive role on colorectal cancer development. In dietary intervention studies Alberts et al and Schatzkin et al showed that a diet rich in fruits and vegetables or wholegrain cereals failed to decrease the risk of new colorectal adenomas.<sup>31,32</sup> They concluded from this that the same interventions would fail to prevent colorectal cancer as well. Similar data were observed in the ECP inter-

vention study.<sup>33</sup> There were some who advocated caution before abandoning the results of former epidemiology. However, some went even further. Indeed Goodled went as far as to label all those who failed to abandon advice on the benefits of dietary fibre as „being in a state of denial“.<sup>34</sup>

Hill et al in 2001, explained why the very common event of new adenoma formation was not a good marker of the much rarer risk of colorectal cancer.<sup>35</sup> Colorectal carcinogenesis is a multistage process, which starts with the formation of a small adenoma. This is a very common event and is normally asymptomatic. There is abundant evidence that the risk factors for adenoma formation often differ from those associated with progression from adenoma through increasingly severe dysplasia to carcinoma.<sup>35</sup> The distribution of adenomas along the colorectum seen at autopsy differs from that of carcinomas<sup>36,37</sup> (Tables 4, 5). In fact, the distribution of adenomas is consistent with a causal agent delivered by the vascular system. In contrast, the distribution of large adenomas and carcinomas, together with the fact that large adenomas regress when the faecal stream is diverted,<sup>38</sup> suggests a causal agent delivered from the colonic lumen, as argued elsewhere.<sup>35</sup>

There are populations with similar adenoma prevalence but different cancer risk and vice versa. There was therefore no good reason to assume that a failure to inhibit the very common event of colorectal adenoma formation indicated a failure to inhibit the unrelated events in progression to carcinoma. The mass of epidemiological evidence should not, therefore, be rejected out of hand on the basis of the previously mentioned studies.<sup>31-33</sup>

One year ago in Lyon the first results of the huge EPIC study were released. This prospective study of more than 500 000 people in 10 European countries dwarfs all previous studies of diet and cancer. The size of the cohort gives great strength to the results obtained (cited in: 39). To date, only cancers from the colon, lung and breast have been reported. The results confirm that the

fruit and vegetable intake is inversely related to colorectal and lung cancer risk. They also confirm the inverse relationship between colorectal cancer risk and fibre intake (cited in: 39).

### Wholegrain cereals

The case that wholegrain cereals protect against cancers at a range of sites has been made by Jacobs et al, Hill, Gerber and La Vecchia and Chatenoud.<sup>40-43</sup> The data for protection mainly come from countries where wheat is the main source of cereals fibre; rice and oats are much less good sources of insoluble fibre but rye may be as good.

People are already advised to eat a high-fibre diet because it helps to prevent a range of diseases and disorders such as heart disease, diabetes, constipation, etc. However, a number of questions remain including:<sup>29</sup>

- How much of one's fibre intake should be from cereals? The best advice is always to get your nutrients from a range of sources. In terms of fibre, probably it would be best to aim for 30-50% from cereals, and most of the rest from vegetables. Fruit do not, in any case, contain much fibre.

**Table 5.** Lack of correlation between the prevalence of colorectal adenomas (% of population) and the risk of colorectal carcinomas per 100 000 per annum, age adjusted (data for males) (Data from Hill; ref. 37).

POPULATION	ADENOMAS	CARCINOMAS
Tromso (Norway)	40	13.2
Oslo (Norway)	34	22.5
Liverpool (UK)	37	31.2
Iran	1	Low
Colombia	7	3.4
Johannesburg (Black)	0	3.8
Japan	9	8.3

**Table 4.** Percentage subsite distribution of adenomas and carcinomas in the large bowel in Sweden (high incidence) and in Colombia (which has a low incidence of colorectal cancer) (Data from Hill; ref. 36).

	SWEDEN		COLOMBIA	
	Adenoma	Carcinoma	Adenoma	Carcinoma
Caecum + ascending colon	24%	20%	18%	30%
Transverse + descending colon	30%	14%	41%	13%
Sigmoid colon	30%	41%	20%	9%
Rectum	16%	24%	21%	48%

- What is „a high intake“ of cereals fibre? The target is 15 g cereal fibre per day.
- How do I achieve that? A normal serving of a high-fibre breakfast cereals contains more than 10-12 g cereal fibre (depending on the brand and the size of the serving) and that would be the basis of a high intake. So the most important thing is to eat breakfast (the easiest way to eat fibre-rich cereals). Then use wholemeal bread in sandwiches or rolls or with meals and the target is easily achievable.
- Which cereals are best? Wheat has the highest content of fibre and appears to be by far the best from the point of view of cancer prevention. In fact the strongest evidence concerns only wheatbran. There are several wheatbran-based cereals. However, oats are also good for your heart, and so for general good health perhaps a mixture is best. Mueslis often contain grains from a variety of sources.

It is important not to eat too much fibre-rich food, because it will disturb the gut. In addition, some people are sensitive to cereals, but they are usually fully aware of that.

### **Meat**

In 1997 the World Cancer Research Fund (WCRF) concluded that there was a relation between red meat consumption and colorectal cancer risk and that “if eaten at all, consumption of red meat should be less than 80 g per day”. In Europe 97% of people eat meat regularly, and so such a recommendation represents a major change in lifestyle. In consequence, since then there have been numerous reviews,<sup>44,45</sup> meetings and workshops<sup>46-48</sup> examining the relation between meat consumption and cancer risk. The conclusion has been that there is little evidence to support such a relationship. There is certainly insufficient evidence to support a recommendation of less than 80 g per day.

In summary, Truswell reviewed 30 case-control studies, of which 20 showed no relationship.<sup>49</sup> Of the remaining 10, only four showed a relationship for both sexes in both colon and rectum. In the other six the relationship reported was for only one sex, or only one of the two sites. He also reviewed 14 cohort studies: 11 showed no relationship, and the other three only showed any relationship at the highest quintile of intake (i.e. more than 140 g per day)! The four European cohort studies all showed no relation between meat intake and colorectal cancer risk,<sup>45</sup> and the latest shows the same result.<sup>50</sup> The pooled analysis of five cohort studies of cancer in vege-

tarians compared with omnivores, and based on 8300 deaths, showed no difference between the two groups in risk of cancer in general or of colorectal or breast cancer in particular.<sup>51</sup> In the UK between 1965 and 1995 the intake of red meat fell by 25%<sup>45</sup> but the risk of colorectal cancer, far from falling proportionately as expected from the WCRF recommendations, actually increased by 50%. In the light of this lack of evidence to support any recommendation on meat and cancer, ECP has not recommendation to change meat consumption.

### **Fish**

There are good theoretical reasons why fish should be protective against cancer. Fish are rich in *n*-3 polyunsaturated fatty acids (pufa), which protect against heart disease, and in animal models protect against cancer of the bowel and breast. The amount of pufa increases as the coldness of the waters from which the fish were caught increases. Such fish oil is also rich in antioxidants which protect the pufa from oxidation, and that too would protect against cancer. There is epidemiological evidence for protection by fish or fish oil against cancer of the bowel.<sup>14,15,52,53</sup>

The amount recommended for protection against heart disease is 2-3 servings per week.

### **Overweight and physical exercise**

Epidemiological studies on risk factors for colorectal cancer have focused mainly on diet.

Weight and height have also been studied, partly because they reflect the balance between energy intake and expenditure in different age periods. Energy intake, body size, physical activity and colorectal cancer risk have been recently reviewed focusing mostly on data coming from Italian, English and Scandinavian studies.<sup>54</sup> Overweight has long been recognized as a risk factor for hormone related and other cancers and this is confirmed not simply from case-control studies but from large cohort studies as well. The major findings of recent Italian studies are that excessive weight at various ages predicts colorectal cancer risk in men while in women, abdominal obesity, as indicated by WHR, represents a more reliable risk indicator.<sup>55</sup> If all men could reduce their BMI below 25, about 9% of male colorectal cancer might be avoided in Italy. A decrease of WHR below 0.82 might reduce colorectal cancer in women by 19%. In addition, the epidemiological evidence consistently shows that physical activity reduces the risk of colon cancer. On the contrary, evidence on rectal cancer is less impressive.<sup>56</sup>

Some uncertainty still exists in relation to the intensity

and duration of physical activity.

Plausible mechanisms by which physical inactivity and obesity may increase the risk of colorectal cancer and female hormone-related cancers have been proposed.<sup>57</sup> Energy imbalance leading to the high body mass may result in a series of metabolic abnormalities; these include high plasma tryceride, glucose and insulin resistance. These features are part of what is known as “syndrome X”. The result may be a physiological milieu that promotes growth generally and of tumor cells specifically, both because of a differential capacity to use glucose (by way of anaerobic metabolic pathways) and an upregulation of receptors for growth factors, including insulin and insulin-like growth factors.

In conclusion, body size control along all life and physical activity represent important factors to prevent colon cancer and a wide range of chronic conditions. Therefore, strategies to favour these goals through counselling from health-care providers, regulatory changes, and programs aimed at individuals and communities should be implemented.

## CONCLUSIONS

From the analysis of the currently available scientific literature on diet and colorectal cancer, it is clearly debatable whether the reliability of any conclusions is sufficient to justify advice being given to the public. Thus, the overall conclusion must be that only the two following recommendations might be considered justifiable in the light of current knowledge:

1. Eat plenty of raw and preserved fruit, salads, vegetables and cereals: there is evidence to suggest that these may be protective against a wide range of digestive cancers and are not positively related to any, although much of the evidence is obtained from observational studies.
2. Maintain a healthy body weight: many cancers as well as many other diseases with a high mortality risk, are associated with overweight. Avoidance of obesity may decrease the risk of cancer at a number of sites (including colorectal cancer) and is unlikely to increase the risk of cancer at any site. Obesity can be avoided by increased exercise or by control of energy intake. More help should be given in encouraging increased exercise, especially in young people, since maintenance of a healthy body weight should ideally be started from an early age.

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