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Conference on ‘Over- and undernutrition: challenges and approaches’

Symposium 1: Overnutrition: consequences and solutions Obesity and cancer risk

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Epidemiological studies have provided convincing evidence that obesity increases the risk for cancers of the oesophagus (adenocarcinoma), colon, pancreas, breast (post-menopausal), endometrium and kidney. The magnitude of the increase in risk varies between cancer sites. For an increase in BMI of 10 kg/m² relative risks are approximately 2.3 for adenocarcinoma of the oesophagus, 1.5 for colon cancer in men, 1.2 for colon cancer in women, 1.4 for post-menopausal breast cancer, 2.9 for endometrial cancer and >1.5 for kidney cancer, while the size of the effect on cancer of the pancreas is uncertain. There is also evidence that obesity increases the risks for cancers of the gallbladder, malignant melanoma, ovary, thyroid, non-Hodgkin lymphoma, multiple myeloma and leukaemia. Estimates of the percentage of cancers that can be attributed to excess body weight suggest that in the UK and similar countries approximately 5% of all cancers are attributable to overweight and obesity.

Obesity: Cancer: Epidemiology

There is now convincing evidence from epidemiological studies showing that obesity increases the risk for several types of cancer, and for the more common cancer sites the estimates of the size of the effect are reasonably precise. The present overview is based on recent reports from expert groups together with the results of meta-analyses and large prospective studies. In turn, the common cancer sites that are clearly related to obesity are discussed, giving examples of relative risk estimates from meta-analyses or large single studies, and some of the mechanisms that may underlie these associations are outlined.

Evidence and methods used

The association between overweight and obesity and cancer risk was evaluated by the International Agency for Research on Cancer in 2002⁽¹⁾. This working group concludes that overweight and obesity definitely increase the risk for cancers of the oesophagus (adenocarcinoma), colon, breast (post-menopausal), endometrium and kidney. A more recent assessment by the World Cancer Research Fund has confirmed the effect of overweight and obesity on these cancer sites and also considers that the evidence

for an adverse effect on cancer of the pancreas is convincing⁽²⁾. The present overview discusses the effects of overweight and obesity on the risk for cancer at these six sites and also summarises the evidence for other types of cancer for which risk is probably also increased by obesity. Most of the estimates of relative risks associated with obesity that are cited in Table 1 are taken from a 2008 meta-analysis⁽³⁾. For breast, endometrial and ovarian cancer in women the estimates are derived from the 2007 report of the Million Women Study, because this single very large study includes detailed adjustments for relevant reproductive and hormonal factors⁽⁴⁾. The results of other large recent studies are discussed when appropriate. For estimates of attributable risks the prevalence of overweight and obesity among men and women aged 55–64 years in England in 2007⁽⁵⁾ have been used.

Oesophageal cancer

Adenocarcinoma of the oesophagus

Obesity increases the risk of adenocarcinoma but not squamous cell carcinoma of the oesophagus. Relative risks

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Table 1. Estimates of the relative risks for cancer at different sites associated with an increase in BMI of 10 kg/m² and of the attributable risks for each site for overweight and obesity in the UK

Type of cancer	Men			Women		
	Relative risk* per 10 kg/m ²	95% CI	Attributable risk‡ (%)	Relative risk* per 10 kg/m ²	95% CI	Attributable risk‡ (%)
Oesophagus adenocarcinoma	2.31	1.77, 3.03	40	2.28	1.72, 3.03	37
Colon	1.54	1.44, 1.64	22	1.19	1.10, 1.28	8
Rectum	1.19	1.12, 1.25	9	NS†	–	–
Gallbladder	NS†	–	–	2.53	1.04, 6.10	41
Pancreas	NS†	–	–	1.25	1.04, 1.49	11
Malignant melanoma	1.37	1.10, 1.69	16	NS†	–	–
Breast, post-menopausal	–	–	–	1.40	1.31, 1.49	16
Endometrium	–	–	–	2.89	2.62, 3.18	46
Ovary	–	–	–	1.14	1.03, 1.27	6
Kidney	1.54	1.32, 1.80	22	1.80	1.56, 2.04	27
Thyroid	1.77	1.08, 2.89	28	1.30	1.12, 1.51	13
Non-Hodgkin lymphoma	1.12	1.06, 1.19	6	1.14	1.00, 1.30	6
Multiple myeloma	1.23	1.10, 1.39	11	1.23	1.14, 1.32	10
Leukaemia	1.17	1.04, 1.30	8	1.37	1.08, 1.74	15
All cancers	1.10	1.04, 1.15	5	1.12	1.09, 1.14	6

*Estimates from Renehan *et al.*⁽³⁾ except for breast, endometrium, ovary and all cancers in women from Reeves *et al.*⁽⁴⁾ and all cancers in men taken as risk for BMI > 30 kg/m² v. BMI 18.5–24.9 kg/m² from Samanic *et al.*⁽¹⁸⁾.

†As the association was not significant it was not reported.

‡Calculated using estimates of the prevalence of overweight and obesity in men and women aged 55–64 years in England in 2007⁽⁵⁾.

for adenocarcinoma of the oesophagus for a 10 kg/m² increase in BMI have been reported as 2.31 among men and 2.28 among women in the 2008 meta-analysis⁽³⁾. Approximately 40% of adenocarcinomas of the oesophagus in the UK may be attributed to overweight and obesity (Table 1).

The mechanism by which obesity increases the risk for adenocarcinoma of the oesophagus is not fully understood, but probably involves an increase in the prevalence of chronic acid reflux from the stomach into the oesophagus, which damages the oesophageal epithelium^(6,7).

Squamous cell carcinoma of the oesophagus

For squamous cell carcinoma of the oesophagus observational studies have reported that the risk is lower in obese subjects than in thin subjects; for example, relative risks for a 10 kg/m² increase in BMI of 0.50 and 0.32 in men and women respectively⁽³⁾. Squamous cell carcinoma of the oesophagus is strongly related to both smoking and alcohol intake. The Million Women Study investigators conclude that residual confounding by smoking and alcohol cannot easily explain the inverse association⁽⁴⁾, but it is possible that the inverse association may be a result of weight loss several years before diagnosis among subjects with preclinical disease.

Colo-rectal cancer

For cancers of the colon and rectum there is strong evidence that the relationship between obesity and risk differs

between men and women⁽³⁾. In men the 2008 meta-analysis reports relative risks for a 10 kg/m² increase in BMI of 1.54 for colon cancer and 1.19 for rectal cancer⁽³⁾. The associations in women are much weaker; a relative risk of 1.19 for colon cancer and no significant association with rectal cancer. Furthermore, there are strongly significant differences in these associations between men and women ($P < 0.0001$ for colon cancer and $P = 0.003$ for rectal cancer). It is also clear that the increase in risk is greater for cancer of the colon than for cancer of the rectum. Furthermore, among women the effect of obesity may be greater among those who are premenopausal; in the Million Women Study the increase in risk for colo-rectal cancer associated with a 10 kg/m² increase in BMI is 1.61 (95% CI 1.05, 2.48) among premenopausal women but 0.99 (95% CI 0.88, 1.12) among post-menopausal women⁽⁴⁾.

Among men in the UK overweight and obesity are responsible for approximately 22% and 9% of cancers of the colon and rectum respectively. Among women overweight and obesity are responsible for approximately 8% of cancers of the colon, with no definite effect on cancers of the rectum (Table 1).

The biological mechanisms by which obesity increases risk of colo-rectal cancer are not understood. Possible mechanisms are that the relatively high circulating insulin levels associated with obesity contribute to increased cell division in the colon⁽⁸⁾ or that the relatively low levels of adiponectin associated with obesity allow increased angiogenesis⁽⁹⁾. Since the effect of obesity varies between men and women, sex hormones may also be involved.

Pancreatic cancer

The evidence on the association between overweight and obesity and the risk for cancer of the pancreas has some inconsistencies. The 2002 assessment by the International Agency for Research on Cancer does not include cancer of the pancreas among the cancers caused by obesity⁽¹⁾, but the 2007 assessment by the World Cancer Research Fund was able to consider more studies and concludes that the evidence is convincing⁽²⁾. The 2008 meta-analysis shows no significant association among men, whereas among women there is a relative risk of 1.25 for a 10 kg/m² increase in BMI⁽³⁾; however, the difference in associations between men and women is not itself significant. Among women the attributable risk for overweight and obesity in the UK is approximately 11% (Table 1).

The mechanism for the effect of obesity on the risk for cancer of the pancreas is not understood. Diabetes mellitus is associated with an increased risk for pancreatic cancer⁽¹⁰⁾ and obesity is a major cause of diabetes, but it is unclear whether diabetes contributes to the causation of pancreatic cancer or whether long-standing changes in the pancreas are precedents of both diabetes and cancer.

Breast cancer

Post-menopausal women

Obesity increases breast cancer risk in post-menopausal women. This relationship is strong among women not using hormone-replacement therapy, but is not evident among women using hormone-replacement therapy⁽¹¹⁾. The Million Women Study investigators report a relative risk of 1.40 for a 10 kg/m² increase in BMI among post-menopausal women who have never used hormone-replacement therapy⁽⁴⁾. Approximately 16% of breast cancers among post-menopausal women in the UK who do not use hormone-replacement therapy are attributable to overweight and obesity (Table 1).

The increase in breast cancer risk associated with obesity among post-menopausal women is probably mediated by oestrogens. In post-menopausal women the main source of circulating oestrogens is conversion from androgens by the enzyme aromatase, which is present in the adipose tissue. Obese post-menopausal women have circulating oestradiol concentrations more than twice as high as those in thin post-menopausal women, and prospective analyses of circulating oestrogen concentrations and breast cancer risk have shown that the increase in risk observed with obesity can be completely explained by the increase in oestradiol concentrations^(12,13). Obesity also causes a reduction in circulating concentrations of sex hormone-binding globulin, leading to an increase in the proportion of oestradiol that is free to leave the circulation⁽¹²⁾.

Premenopausal women

Obesity is associated with a reduction in breast cancer risk among premenopausal women. The Million Women Study investigators report a relative risk of 0.86 for a 10 kg/m²

increase in BMI among premenopausal women⁽⁴⁾, and the results of the 2008 meta-analysis are almost identical⁽³⁾.

The reason for the inverse association between obesity and breast cancer risk among premenopausal women is poorly understood. There is some evidence that obesity frequently leads to anovular menstrual cycles, which may reduce the risk for breast cancer as a result of lower exposure to progesterone⁽¹⁴⁾, but other mechanisms could be involved. It should also be noted that obesity in premenopausal women is likely to lead to obesity throughout life and therefore to an eventual increase in breast cancer risk.

Endometrial cancer

Obesity causes a large increase in the risk for endometrial cancer. The Million Women Study reports a relative risk for a 10 kg/m² increase in BMI, with full adjustment for potential confounding factors including reproductive history, of 2.89⁽⁴⁾. Analyses subdivided by menopausal status at recruitment show a relative risk of 1.77 among premenopausal women and 3.98 among post-menopausal women, and this difference in the size of the risks is significant ($P = 0.0001$). Approximately 46% of endometrial cancers among post-menopausal women in the UK can be attributed to overweight and obesity (Table 1).

As with breast cancer, the effect of obesity in post-menopausal women on the risk for endometrial cancer is probably mediated by the increase in serum concentrations of oestradiol and the reduction in serum concentrations of sex hormone-binding globulin; in premenopausal women the mechanism may involve an increase in the incidence of anovulation and consequent increased exposure to oestradiol unopposed by progesterone⁽¹⁵⁾.

Kidney cancer

Overweight and obesity substantially increase the risk for kidney cancer. The 2008 meta-analysis estimates increases in risk per 10 kg/m² increase in BMI of 1.54 and 1.80 in men and women respectively⁽³⁾. Approximately one-quarter of kidney cancers in the UK may be attributable to overweight and obesity (22% in men and 27% in women; Table 1). Despite this well-established association the biological mechanism is not known. High blood pressure is strongly associated with obesity and is a risk factor for kidney cancer, but the evidence suggests that these factors may have independent effects on the risk for kidney cancer^(16,17).

Other cancers

The 2008 meta-analysis reports significant associations between obesity and increased risks for cancers of the gallbladder (in women), malignant melanoma (in men), thyroid, non-Hodgkin lymphoma, multiple myeloma and leukaemia⁽³⁾. The Million Women Study also reports a significant increase in the risk for ovarian cancer associated with obesity⁽⁴⁾. The estimates of relative risks for these associations are shown in Table 1; further evaluation

of these associations is required, but it is likely that obesity does increase the risk for most if not all these cancers.

Observational studies show that the risk for lung cancer is relatively high among individuals with a low BMI, but this finding may be a result of residual confounding by smoking and reverse causality^(3,4). Obesity has little or no effect on the risk for stomach cancer or prostate cancer^(3,4).

All cancers combined

Some studies have examined the association between obesity and the risk for any type of cancer. Two very large cohort studies provide reliable information. Among 360 000 Swedish men in the construction industry the relative risk in obese men compared with normal-weight men for any type of cancer is 1.10⁽¹⁸⁾. In the Million Women Study in the UK the relative risk for any type of cancer (except non-melanoma skin cancer) associated with a 10 kg/m² increase in BMI is 1.12⁽⁴⁾. Thus, the attributable risks for all cancers in the UK are approximately 5% and 6% among men and women respectively (Table 1).

Reversing the effect of obesity on cancer risk

The clear evidence that overweight and obesity increase the risk for several types of cancer implies that weight loss should, at least to some extent, reverse this effect. There is some epidemiological evidence to support this notion; for example, the Nurses' Health Study has shown that women who lose weight after the menopause are at lower risk for breast cancer than women who maintain their weight⁽¹⁹⁾. At a population level there is very little evidence that reducing obesity leads to reduced cancer rates, largely because of the lack of effective public health strategies to reduce obesity. There is some evidence from recent clinical studies that surgical procedures that cause substantial weight loss among morbidly-obese patients are associated with reduced cancer risk^(20,21).

Future research questions

More data are required on the possible associations between overweight and obesity and the risk for less-common types of cancer. There is also a need to explore further the importance of obesity at different ages in relation to lifetime risk for cancer and to better understand whether the distribution of body fat is important as well as the extent of adiposity.

Conclusions

Obesity is an important cause of cancer. The largest effects and greatest attributable risks are for adenocarcinoma of the oesophagus and for endometrial cancer. Current estimates suggest that approximately 5% of cancers in the UK are caused by overweight and obesity (Table 1). The percentage is likely to be similar in other Western countries with a similar prevalence of obesity and will increase if the prevalence of obesity increases. A reduction in cancer rates

would be among the many benefits that would result if the prevalence of obesity can be reduced.

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