Chapter 5
Cancer-preventive effects

Human studies

In view of the large number of epidemiological studies of effects of body weight and adiposity on cancer, the following review focuses on what the Working Group deemed to be the most informative ones. In general, they are those in which the analysis was based on larger numbers of cases (usually over 100), though the cut-off used varies from 200 cases for the most studied cancer sites to only 50 for some others.

A single cohort study has often generated a number of publications over many years, with longer follow-up and thus more cases. Likewise, data from case–control studies are often further analysed to examine new measures or address new issues. Only the latest follow-up from cohort studies is generally discussed or presented in the tables and further analyses of case–control data are considered only if they provide important new information.

Methodological considerations

Epidemiological studies are critical to the evaluation of weight control and physical activity in relation to cancer incidence because they address the effects of these variables, over a realistic range of exposures, on the endpoints of direct interest to humans. Randomized trials, which in theory might provide superior data, have not been conducted and may never be, due to the difficulty of maintaining informative contrasts in exposure among large populations for many years. This section highlights some of the methodological issues surrounding study design, sources of bias, measurement of adiposity and physical activity, and the interpretation of findings.

Positive energy balance cannot be measured directly in large epidemiological studies but in theory can be estimated by examining its components: energy intake and expenditure. However, neither of these components can be well estimated by existing self-reporting methods, and one of the most valid measures of recurrent positive energy balance in humans remains adult weight gain.

Recall bias

Many factors can influence the recall or reporting of weight and physical activity. This is potentially most serious in case–control studies, because even small differences in over- or under-reporting by cases compared with controls can seriously influence the observed associations.

Selection bias

Biased associations can also occur if persons who participate as controls are more likely to be health-conscious, and thus more likely to be physically active and lean, than those who do not participate. This would tend to produce erroneous positive associations with obesity and inverse associations with physical activity. If potential control subjects are truly a representative sample of the population from which the cases arose and participation rates are high, selection bias is minimal. However, participation rates have declined progressively over time in many countries, so that the potential for selection bias has become increasingly serious. Both recall and selection biases are avoided in prospective studies.

Detection bias

For some cancers that can be detected by a screening test, such as early prostate cancer diagnosed by screening for prostate-specific antigen (PSA), bias may exist in either case–control or cohort studies if the likelihood of screening is associated with other health-conscious behaviour. Studies of only fatal endpoints, rather than incident cancers, can be misleading if body weight or activity affects prognosis or is correlated with behaviours that lead to earlier diagnosis or better compliance with treatment. These concerns are not important for cancers that are almost always fatal, such as cancers of the pancreas or lung or for which early diagnosis and treatment have little effect.

Publication bias

Failure of investigators to report or of journals to publish negative findings on physical activity or weight could result in a biased conclusion based on the available literature. Pooled analyses in which the studies were selected for reasons other than having data on weight or activity should not be susceptible to this form of bias.

Confounding

People who conscientiously exercise and successfully control their weight often have healthier lifestyles than those who do not. Furthermore, high physical activity is associated with low socioeconomic status, which, in turn, is correlated with increased or decreased cancer risk,

depending upon site. Cigarette smoking is a particularly important confounding variable, as it is a strong cause of many cancers and is less common among exercising individuals but more frequent among lean persons, in part due to its mild anorectic effect. Thus, if smoking is not taken into account, physically active and overweight persons appear to have lower rates of many cancers, even if weight and physical activity have no direct effect. In evaluating the results of epidemiological studies, the degree to which the results have been adjusted for potentially confounding variables is an important consideration.

In this report, the independent effects of body weight and physical activity are of particular interest. Because regular physical activity is an important method of controlling weight, these variables tend to be inversely correlated. While it is often of interest to mutually control the effects of weight and physical activity for each other to determine the degree to which they are independently associated with cancer risk, the results should be interpreted cautiously. For example, an observation that physical activity was associated with cancer risk before, but not after, controlling for body weight would not mean that physical activity has no effect. The most likely interpretation would be that the effect of physical activity is mediated by its influence on weight.

Reverse causation

In evaluating associations between weight or physical activity and cancer incidence, the direction of causality should be carefully considered. Preclinical cancer is a well-known cause of weight loss and may also lead to a reduction in physical activity. In addition, factors such as cigarette smoking or occupational factors that cause both chronic lung disease and some cancers can lead to changes in weight and activity years before the diagnosis of cancer. Merely controlling statistically for smoking may not be adequate to account for reverse causation, because nuances of smoking habits or susceptibility to cigarette smoke are not taken into account. Analytical strategies such as restriction to never-smokers or allowing a long lag time between the assessment of weight or activity and diagnosis of cancer can be helpful.

Studies of weight loss and risk of cancer are particularly problematic because relatively few healthy persons in a population successfully lose weight and maintain their loss, so that statistical power is low. More seriously, in epidemiological studies, these healthy persons are usually impossible to distinguish from those who have lost weight due to cancer or chronic disease that may be the result of smoking or other factors.

Generalizability

Most reported studies of weight and physical activity in relation to cancer incidence have been based on Caucasian populations of Europe and North America. Part of the incompleteness of information from other areas of the world is due to a lack of tested methods for assessing physical activity in different cultures. Also, the lack of knowledge about personal weight and height in societies where scales are not widely available can make case–control studies of these relationships impossible, because they typically depend on self-reported measures several years before diagnosis. This is unfortunate because, as is discussed in the section on breast cancer, some relationships with body weight appear to differ between high- and low-risk populations. These differences are unlikely to be the result of genetic factors, because rates of most cancers converge when various ethnic groups live in similar environments. A more likely explanation is that the relationship of body weight and physical activity to cancer risk depends on the range of these variables present in a population and interactions with other aspects of lifestyle and diet.

Measurement of weight and physical activity

Studies of weight and physical activity depend directly on valid measures of these variables. Issues of validity are discussed in detail in Chapter 1, but some issues particularly relevant to epidemiological studies are mentioned below.

Measurement of weight: Weight is commonly used in epidemiological studies among adult populations as an indirect measure of adiposity. Adjustment for height, most often by calculating BMI, removes variation in weight due to height and thus improves the correlation with body fat mass. Although use of BMI does not allow distinction between lean and fat mass, in most general populations, the majority of the variation is due to adiposity. Thus, correlations of BMI with body fat mass adjusted for height measured by underwater weighing have been approximately 0.9 (Spiegelman *et al.*, 1992; Willett, 1998). In populations where scales are widely available, self-reported weights are commonly used in epidemiological studies. There is some tendency for overweight persons to under-report weight and for underweight persons to over-report weight. However, self-reported weights have been shown to be highly valid, being strongly correlated with measured weights (correlations typically over 0.95), and to be consistently predictive of diseases known to be related to excessive adiposity (Willett, 1998). Even when referring to periods many years in the past, self-reported weight and height have been shown to retain a high degree of validity. Because use of self-reported data on weight and height is necessary in most case–control studies to avoid the influence of cancer on weight, and these are the only feasible measures in some prospective studies, the majority of information on adiposity and cancer risk is obtained in this way. In populations engaged in heavy physical labour, as

in some developing countries, it is possible that BMI may reflect adiposity less well.

Other measures of adiposity used in epidemiological studies include changes in weight, skinfold and abdominal and hip circumferences, each of which provides somewhat different information. Changes in weight from, for example, age 20 years to midlife, can be particularly useful because they take into account possible differences in frame size, and increases are largely due to changes in body fat unless a person has consciously engaged in body-building. Changes in weight also are simple and readily interpretable by the public.

Measurement of physical activity: Physical activity involves many components, including the *type* of activity (i.e., occupational, recreational, household), the *dose* of the activity (i.e., frequency, intensity and duration) and the *time period* in life when it is measured. These components of physical activity have been measured using widely different methods in epidemiological studies. Some of the inconsistencies in results obtained by these studies may be attributable to these differences in the methods used. Furthermore, since the underlying biological mechanisms involved in the disease process were largely unknown when these studies were conducted, the relevant types of activity and time periods in life when these activities were performed may not have been adequately captured.

Errors in measuring physical activity tend to lead to underestimation of the strength of associations with cancer risk. Many early studies used crude methods for assessing activity and were sometimes only based on occupation. Most recent studies have used physical activity questionnaires that are more detailed and comprehensive in the types of activity evaluated. Differences in the degree of validity of various questionnaires lead to differences in estimates of associations with cancer risk. However, even a highly valid questionnaire that is directed to a time period not relevant to the development of cancer may fail to detect an important effect of physical activity. Thus, questionnaires that assess activity at various periods in life, and repeated assessments of physical activity in prospective cohort studies, can be particularly informative.

Studies that have evaluated the validity of recalled activity have shown that more intense activities are recalled with greater accuracy than moderate activities. Consequently, the ability to detect stronger associations for intense activity, as shown in some studies particularly of colon cancer, may reflect more accurate measurement of these activities. However, it is also possible that associations with vigorous activity reflect important biological mechanisms.

Measures of physical activity assessed by standardized questionnaires as used in recent epidemiological studies have been shown to be correlated with biological measurements such as resting pulse and treadmill assessments of fitness (see Chapter 1). Moreover, these measurements have been associated with future risks of cardiovascular disease and diabetes in prospective studies. When physical activity as assessed by questionnaires has been compared with that recorded in detailed activity diaries, correlations have been approximately 0.5 to 0.6 (Wolf *et al.*, 1994; Chasan-Taber *et al.*, 1996). Thus, it is clear that the methods of assessing activity in epidemiological studies are providing informative data, but the magnitude of the associations tends to be underestimated. The correlations with detailed diaries suggest that the strength of an observed relative risk will be about half of the true relative risk (Willett, 1998).

Modification of associations by other factors

In this evaluation, we consider evidence that associations between physical activity or weight and cancer incidence may be modified by other variables including gender, age or family history. Ideally, genetic factors based on DNA markers might be examined as modifiers, but little such work has been done up to now. In general, an ability to examine these interactions requires large sample sizes, which have often not been available. However, the evaluation of associations within population subgroups can also provide insight on possible mechanisms. For example, the finding that the association between BMI and post-menopausal breast cancer is largely absent among women currently using estrogen replacement treatment (which results in high blood estrogen levels in all women regardless of their BMI) adds to evidence that the effect of obesity on post-menopausal breast cancer is largely mediated by endogenous estrogens.

Considerations in assessing causality

Whether associations observed in epidemiological studies should be considered to be causal has been much discussed (Tomatis, 1990). Here we do not consider international correlations (ecological studies) relating population average values of weight or physical activity to cancer rates, because these associations are likely to be seriously confounded by a multitude of factors associated with economic development. In reviewing the case–control and cohort studies, particular attention is paid to the consistency of findings across a range of populations, the statistical robustness of associations as reflected by confidence intervals, and the degree to which potentially confounding factors have been accounted for.

Weight and weight control

Colorectal cancer

This review summarizes what is known about the relationships between body weight and the risk for both colorectal

cancer and colorectal adenomas, the pre-malignant lesion for colorectal cancer. The evidence for an overall association is examined, as well as the patterns by gender, by colorectal subsite and by stage of carcinogenesis. The possible biological mechanisms underlying such an association and how the interrelated risk factors of physical activity and dietary energy intake (Potter, 1996; Hill, 1998) might contribute independently or along the same causal pathway with obesity are discussed later in this chapter.

Colorectal cancers arise predominantly from adenomas, a process that in most people takes at least 10 years (Vogelstein *et al.*, 1988; Kronborg & Fenger, 1999). Small adenomas first develop from mutated normal colonic epithelium, then some of the small adenomas grow in size and become more histologically abnormal with successive mutations, until finally invasive cancer develops. Body weight may have effects on colorectal cancer risk at any of these stages, including initiation, promotion and progression, over a 10–15-year period or longer. Inferences about point(s) in the development of colorectal cancer at which obesity might be relevant can be made by examining not only the existence of an association between body fatness and colorectal cancer, but also the pattern of association with lifetime weight history, and whether that association differs by adenoma size.

Several very large case–control and cohort studies have reported not only on the overall association between measures of body fatness and colorectal cancer but also, with substantial power, findings stratified by subsite within the colorectum and by gender. Some have also added measures of body fat distribution, often as the WHR, in order to investigate whether body fat distribution acts as a cancer risk factor independent of overall adiposity, as is often estimated by the BMI. There is extensive literature on body fatness indicators near the time of diagnosis, but much less evidence concerning lifetime weight patterns.

This review does not attempt to describe all published studies. Only the larger studies are included and only those that have presented evidence regarding a dose–response relationship between BMI and colorectal neoplasia. Studies that presented only average BMI levels for case and comparison groups are not included. For studies that have generated several reports, the report presenting the greatest detail on body weight or the most recent update (e.g., from ongoing cohort studies) has been reviewed. Studies relating body weight to adenomas are less numerous, so the review is less selective. Thus for colorectal cancer, only studies with more than 200 cases were included, while for adenomas, studies with as few as 100 cases are included.

Body mass index

The associations between BMI, body weight changes and body fat distribution are summarized separately for colon and rectal cancer, but there are only a small number of studies of rectal cancer (Table 23). Several studies have presented findings by subsite of the colon in which the cancer arose. Findings from studies of BMI and adenomas are also presented in Table 23, since they can provide evidence regarding the time(s) in colorectal carcinogenesis when factors associated with body weight might be most important.

Cohort studies

Despite some variation, cohort studies generally show positive associations between body fatness, as indicated by the BMI, and risk of colorectal cancer. Across the cohort studies, there is about a 50–100% higher risk in the highest quartile of BMI compared with the lowest quartile. Different BMI cut-points have been used, but the strength of the association corresponds in most studies to nearly a doubling of risk in those with BMI of 30 kg/m^2 or over compared with those having a BMI under 23 kg/m^2. Most studies have found a trend of increasing colon cancer risk with increasing BMI across a wide range, with no clear evidence for a threshold effect. The cohort study by Chyou *et al.* (1994), which found the smallest relative risk (RR = 1.2; 95% CI 0.87–1.7), was conducted among Asian men living in Hawaii, and the difference in BMI between the groups compared was narrow (>26 vs <22 kg/m^2). Whether the weaker association was due to this lower distribution of BMI values in that population or to other factors is unknown.

The observed association between BMI and colorectal cancer risk is generally more consistent and of higher strength for men than for women. The strength of the association is nearly twice as high for males as for females in studies that have presented results for both. For example, in a large cohort study of cancer mortality conducted by the American Cancer Society (Murphy *et al.*, 2000a), the relative risks associated with a BMI in the obese range (above 30 kg/m^2) compared with a BMI below 25 kg/m^2 were 1.8 for men and 1.2 for women. There is also a pattern of a positive association of about the same strength between BMI and colon adenomas. A cohort study of male health professionals (Giovannucci *et al.*, 1995) reported no association between adenomas and BMI, but the findings were not presented in detail. Among the adenoma studies, the differences between the genders seem less than for cancer, although there are too few such studies to allow a firm conclusion to be drawn. For studies that assessed the association with BMI separately for larger and smaller adenomas, the pattern suggests that the association is stronger for larger adenomas. For example, in a cohort study of US nurses (Giovannucci *et al.*, 1996), the relative risk for overweight was 2.2 (95% CI 1.2–4.2) for large adenomas, but only

Table 23. Studies of body mass index and risk of colorectal neoplasia

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend*	Adjustment for confounding	Comments
Colon cancer, cohort studies							
Lee & Paffenbarger (1992a), USA	1962–88	M 290	≥26 vs < 22.5 (5)	1.5 (1.1–2.1)	Yes	Age, physical activity, family history	Harvard alumni
Bostick *et al.* (1994), USA	1986–90	F 212	>30.6 vs < 22.9 (5)	1.4 (0.90–2.2)	Yes	Age, energy intake, height, parity, two nutrients	Age 55–69 years
Chyou *et al.* (1994), USA	1965–92	M 289	≥26 vs < 22 (4)	1.2 (0.87–1.7)	Yes	Age	Japanese living in Hawaii
Giovannucci *et al.* (1995), USA	1986–92	M 203	≥29 vs < 22 (5)	1.5 (0.89–2.5)	Yes	Age, height, physical activity, screening, family history, smoking, NSAIDs, five foods/nutrients, alcohol	Health professionals
Martinez *et al.* (1997), USA	1980–92	F 393	≥29 vs <21 (5)	1.4 (1.0–2.1)	Yes	Age, smoking, family history, physical activity, hormone replacement therapy, NSAIDs, alcohol, red meat	Nurses
Ford (1999), USA	1971–92	M 104 F 118	≥30 vs <22 (6)	3.0 (0.99–8.7) 2.7 (1.0–7.2)	Yes Yes	Age, race, smoking, education, cholesterol, physical activity, alcohol	Age 25–74 years
Murphy *et al.* (2000a), USA	1982–94	M 1792 F 1616	≥30 vs <25 (3)	1.8 (1.5–2.0) 1.2 (1.1–1.5)	Yes No	Age, race, education, smoking, physical activity, alcohol, NSAIDs, family history, hormone replacement therapy, three foods/nutrients	Mortality study
Rectal cancer, cohort studies							
Le Marchand *et al.* (1992), USA	1972–86	M 203	Highest vs lowest tertile	0.8 (0.5–1.2)	No	Age, socioeconomic status	Hawaii residents
Colorectal adenoma, cohort studies							
Giovannucci *et al.* (1996), USA	1976–92	F 178 F 125	≥29 vs < 21 (5)	1.4 (0.86–2.4) 2.2 (1.2–4.2)	No Yes	Age, family history, screening, smoking, NSAIDs, four foods/ nutrients, alcohol	Small adenomas Large adenomas By colonoscopy

Table 23 (contd)

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend	Adjustment for confounding	Comments
Colon cancer, case–control studies							
Graham *et al.* (1988), USA	1975–84	M 205 F 223	Highest vs lowest quartile	2.2 (1.2–4.0) 1.8 (1.0–3.4)	Yes Yes	Age, race	Population-based
Gerhardsson de Verdier *et al.* (1990b), Sweden	1986–88	M 233 F 271	>26.5 vs < 21.4 (5)	2.8 (1.3–6.0) 1.5 (0.9–2.7)	Yes Yes	Age	Population-based
Kune *et al.* (1990), Australia	1980–81	M 388 F 327	> 31 vs 20–25 (3) > 31 vs 19–24 (3)	1.2 (0.50–2.9) 0.73 (0.30–1.6)	Yes No	Age, dietary risk index	Population-based
Dietz *et al.* (1995), USA	1990–91	F 758	Weight > 72.6 kg vs <58.1 kg (4)	1.3 (1.0–1.7)	Yes	Height, age, family history, screening	Population-based
Le Marchand *et al.* (1997), USA	1987–91	M 698 F 494	>26 vs <22 (4) >26 vs <21 (4)	2.2 (1.5–3.2) 1.2 (0.8–1.9)	Yes No	Age, family history, alcohol, smoking, energy intake, three foods/nutrients, physical activity	Colorectal cancer Population-based
Caan *et al.* (1998), USA	1991–94	M 1095 F 888	Highest vs lowest quintile	2.0 (1.5–2.6) 1.4 (1.1–1.9)	Yes Yes	Age, NSAIDs, energy intake, fibre, calcium, family history, physical activity	Population-based
Russo *et al.* (1998), Italy	1992–96	M 687	≥25 vs < 25 (2)	1.2 (1.0–1.5)	NE	Age, education, physical activity, energy intake	Colorectal cancer Hospital-based
Rectal cancer, case–control studies							
Gerhardsson de Verdier *et al.* (1990b), Sweden	1986–88	M 106 F 109	>26.5 vs <21.4 (5)	1.7 (0.7–4.0) 1.0 (0.5–1.9)	No No	Age	Population-based
Dietz *et al.* (1995), USA	1990–91	F 239	Weight > 72.6 kg vs < 58.1 kg (4)	1.1 (0.7–1.7)	No	Height, age, family history, screening	Population-based
Le Marchand *et al.* (1997) USA	1987–91	M 221 F 129	Highest vs lowest tertile	2.9 0.8	Yes No	Age, family history, alcohol, smoking, energy intake, three foods/nutrients, physical activity	Population-based

Table 23 (contd)

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend	Adjustment for confounding	Comments
Russo *et al.* (1998), Italy	1992–96	M 437	≥25 vs < 25	1.1 (0.88–1.4)	NE	Age, education, physical activity, energy intake	Hospital-based
Colorectal adenoma, case–control studies							
Neugut *et al.* (1991), USA	1986–88	M 174 F 127	≥ 27.1 vs ≤23.1 (4) ≥ 33.5 vs ≤26.5 (4)	1.4 (0.8–2.5) 2.1 (1.1–4.0)	No Yes	Age	By colonoscopy
Shinchi *et al.* (1994), Japan	1991–92	M,F 228	>26.95 vs < 22.5 (4)	1.9 (1.2–3.0)	No	Smoking, acohol, physical activity	By colonoscopy; age 49–55 years
Davidow *et al.* (1996), USA	1986–88	M 139	≥ 29.1 vs <24.4 (4)	1.9 (0.9–4.0)	No	Age, smoking, physical activity, energy intake	By colonoscopy
Bird *et al.* (1998), USA	1991–93	M,F 339 M,F 139	Highest vs lowest quartile	1.6 (0.9–2.6) 2.5 (1.1–5.4)	No Yes	Age, sex, smoking, NSAIDs, physical activity, energy intake, fibre	Small adenomas Large adenomas By colonoscopy
Kono *et al.* (1999), Japan	1995–96	M 189	≥ 26.9 vs < 22.45 (4)	2.4 (1.1–5.1)	No	Smoking, alcohol	By colonoscopy; age 47–55 years

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories

1.4 (95% CI 0.86–2.4) for small adenomas.

Case–control studies

As seen in the cohort studies, the case–control studies of BMI and colon cancer risk show a pattern of association across most studies, with a stronger association for men than for women. Six case–control studies that used identical methods to study men and women found a stronger association between BMI and colorectal cancer among men (Graham *et al.*, 1988; Gerhardsson de Verdier *et al.*, 1990b; Kune *et al.*, 1990; Le Marchand *et al.*, 1997; Caan *et al.*, 1998; Russo *et al.*, 1998). Case–control studies also show an association between BMI and adenoma risk of a similar magnitude to that seen for colon cancer, though in the single study that reported separately for men and women (Neugut *et al.*, 1991), the gender difference seen for colon cancer was not observed. The RR was higher for women.

The association between colorectal cancer risk and body weight is, in general, stronger and more consistently observed for cancers of the distal colon than for those of the proximal colon, among both men and women, especially in the very large studies (Dietz *et al.*, 1995; Le Marchand *et al.*, 1997; Caan *et al.*, 1998; Russo *et al.*, 1998). In contrast to the findings for colon cancer, studies of rectal cancer have generally shown little or no evidence for an association with BMI (Gerhardsson de Verdier *et al.*, 1990b; Russo *et al.*, 1998).

Weight change

Findings from studies that have examined the relationship between lifetime weight history and colon cancer risk are summarized in Table 24. These studies have reported colorectal cancer risks in relation to both BMI in early adulthood and BMI during later adult years, nearer the time of onset of cancer diagnosis. For only a few studies were direct estimates presented for the association between weight gain *per se* and colon cancer risk (Dietz *et al.*, 1995; Le Marchand *et al.*, 1997; Kono *et al.*, 1999; Russo *et al.*, 1999).

Cohort studies

In general, cohort studies have not yielded evidence suggesting a stronger association between BMI earlier in life and colorectal neoplasia than for BMI later in life (Table 24). The studies by Lee & Paffenbarger (1992a) and Le Marchand *et al.* (1992) both showed similar relative risks for BMI in the late second and the third decades of life to those for BMIs in later adulthood (all in the range1.4 to 1.6).

Case–control studies

Case–control studies do suggest that elevated BMI in the later adult years and weight gain between early adult ages and later adult ages increase risk for colon cancer (Dietz *et al.*, 1995; Le Marchand *et al.*, 1997), although this is less clear for adenomas (Bird *et al.*, 1998; Kono *et al.*, 1999). As in the cohort studies, there is no suggestion that body weight earlier in life is more important as a predictor of colon cancer risk than is body weight later in life.

Body fat distribution

Body fat distribution seems to be an additional predictor of chronic disease risk beyond the effect of overall obesity. Table 25 displays the evidence for an association between measures of body fat distribution and colon cancer risk. All studies expressed body fat distribution as the WHR, except for one which used the ratio of subscapular to triceps skinfold thickness (S/T ratio), another index of central adiposity (Ford, 1999).

Cohort studies

The relative risks or odds ratios for colorectal neoplasia associated with high versus low or normal levels of WHR are shown in Table 25. The ranges and distributions of WHR and of the S/T ratio differ substantially across the various cohort studies, but as was observed with BMI, the WHR shows a pattern of a positive association with both colorectal cancer and colorectal adenoma risk. However, the single study using the S/T ratio did not find an association (Ford, 1999). In the studies reporting dose–response patterns, there was no specific threshold for this association except in the study of males by Giovannucci *et al.* (1995). As was seen for BMI, there is also an association between WHR and adenoma risk in cohort studies, which in one study was stronger for large adenomas.

Case–control studies

Like the cohort studies, case–control studies show an elevation of risk with higher WHR levels of a similar magnitude to the association with elevated BMI.

Discussion

High levels of body fat, as indicated by higher BMI during adult life and/or higher WHR, are associated with increased risk for colon cancer and for colon adenomas. This association is seen for both men and women, though the association with BMI is higher among men. The reason for this gender difference is unknown. If obesity was simply an indicator of energy imbalance, there should be no difference between the genders. On the other hand, there may be an offsetting beneficial effect of obesity among women. A factor such as the hyper-estrogenaemia that is associated with postmenopausal obesity could be responsible, as an estrogen benefit could serve to diminish the obesity-related risk in women. This hypothesis is further discussed later in this chapter.

The observation that BMI is more strongly associated with larger adenomas than with smaller adenomas suggests that obesity-related factors may act at a later stage in the development of cancer, perhaps by contributing to the

Table 24. Studies of weight change and risk of colorectal neoplasia

Author, date, study location	Study dates	No. of cases	BMI, Young adult ages		BMI near time of diagnosis		Adult weight change		Adjustment for confounding
			BMI range contrasts (no. of categories)	RR (95% CI)	BMI range contrasts (no. of categories	RR (95% CI)	BMI range contrasts (no. of categories)	RR (95% CI)	
Colon cancer, cohort studies									
Lee & Paffenbarger (1992a), USA	1962–88	M 266	>23.5 vs < 20 in college (5)	1.4 (0.99–2.0)	>26 vs <22.5 at age 47 (5)	1.5 (1.1–2.2)	NA	NA	Age, physical activity, family history
Le Marchand *et al.* (1992), USA	1942–86	M 203	Highest vs lowest tertile at age 15–29	1.6 (1.2–2.1)	Highest vs lowest tertiles at age 45–59	1.4 (1.1–1.8)	NA	NA	Age, socio-economic status
Rectal cancer, cohort studies									
Le Marchand *et al.* (1992), USA	1942–86	M 203	Highest vs lowest tertile at age 15–29	0.7 (0.6–1.4)	Highest vs lowest tertiles at age 45–59	0.8 (0.5–1.2)	Highest vs lowest tertiles, age 15–45 change	1.2 (0.8–1.8)	Age, socio-economic status
Colorectal adenoma, cohort studies									
Giovannucci *et al.* (1996), USA	1976–92	F 125	Highest vs lowest quintile at age 18	1.9 (1.1–3.5)	≥29 vs <21 (5)	2.21 (1.2–4.2)	NA	NA	Age, family history, screening, smoking, NSAIDs, four foods/ nutrients, alcohol Large adenomas
Colon cancer, case–control studies									
Dietz *et al.* (1995), USA	1990–91	F 737			>72.6 kg vs <58.1 kg 5 y ago (4)	1.3 (1.0–1.7)	>23% gain vs <6% since age 18 (4)	1.3 (1.0–1.6)	Age, weight at 18 y, height, family history, screening
Le Marchand *et al.* (1997), USA	1987–91	M 698	>23 vs <20 at age 25 (4)	1.5 (1.0–2.2)	26 vs <22 5 y ago (4)	2.2 (1.5–3.2)	>14 kg gain vs <2 kg age 25 to 5 y ago (4)	1.6 (1.0–2.4)	Age, family history, alcohol, smoking, energy intake, three foods/nutrients, physical activity
		F 494	>22 vs <19 at age 25 (4)	1.5 (0.9–2.3)	>26 vs <21 5 y ago (4)	1.2 (0.8–1.9)	>11 kg gain vs <2 kg age 25 to 5 y ago (4)	0.8	

Table 24 (contd)

Author, date, study location	Study dates	No. of cases	BMI, Young adult ages: BMI range contrasts (no. of categories)	BMI, Young adult ages: RR (95% CI)	BMI, near time of diagnosis: BMI range contrasts (no. of categories)	BMI, near time of diagnosis: RR (95% CI)	Adult weight change: BMI range contrasts (no. of categories)	Adult weight change: RR	Adjustment for confounding (95% CI)
Colorectal cancer, case–control studies									
Russo *et al.* (1998), Italy	1992–96	M 1124	>28.1 vs <22.5 at age 30 (5)	1.8 (1.3–2.4)	>28.7 vs <22.5 at age 50 (5)	1.7 (1.3–2.3)	Age 30–50 change (vs no change)		Age, education, physical activity, energy intake
							Men – decrease	1.1 (0.88–1.4)	
		F 819		1.3 (0.97–1.7)		0.92 (0.68–1.2)	Men – increase	0.75 (0.63–0.88)	
							Women – decrease	0.93 (0.71–1.2)	
							Women – increase	0.66 (0.54–0.80)	
Rectal cancer, case–control studies									
Dietz *et al.* (1995), USA	1990–91	F 234			>72.6 kg vs <58.1 kg 5 y ago (4)	1.1 (0.7–1.7)	>23% gain vs <6% since age 18 (4)	1.0 (0.7–1.5)	Age, weight at 18 y, height, family history, screening
Le Marchand *et al.* (1997), USA	1987–91	M 221	Highest vs lowest tertile at age 35	2.0	Highest vs lowest tertile 5 years ago	2.9			Age, family history, alcohol, smoking, energy intake, three foods/nutrients, physical activity
		F 129		1.4		0.8			
Colorectal adenoma, case–control studies									
Bird *et al.* (1998), USA	1991–92	483	Highest vs lowest quartile at age 18	1.1 (0.8–1.6)	Highest vs lowest quartile 5 years ago	1.3 (0.9–1.9)	Highest vs lowest quartile, weight gain or weight loss over last 10 years	1.8 (0.7–4.4)	Sex, age
Kono *et al.* (1999), Japan	1995–96	M 189	>26.5 vs <22.25 10 yrs ago	1.5 (0.7–3.1)	>26.9 vs <22.4 (4)	2.4 (1.1–5.1)	>6 kg gain vs ≤2 in past 10 yrs (4)	2.2 (1.0–4.8)	Smoking, alcohol

NA, not analysed

Table 25. Studies of body fat distribution and risk of colorectal neoplasia

Author, date, study location	Study dates	No. of cases	WHR range contrasts (no. of categories)	Relative risk (95% CI)	Trend*	Adjustment for confounding	Comments
Colon cancer, cohort studies							
Bostick *et al.* (1994), USA	1986–90	F 211	>0.91 vs <0.76 (5)	1.2 (0.83–1.9)	No	Age, energy intake, height, parity, two nutrients	Age 55–69 y
Giovannucci *et al.* (1995), USA	1986–92	M 117	> 0.99 vs <0.90 (5)	3.4 (1.5–7.7)	Yes	Age, screening, family history, smoking, physical activity, NSAIDs, five foods/nutrients, alcohol	Health professionals
Martinez *et al.* (1997), USA	1980–92	F 161	>0.83 vs <0.73 (5)	1.5 (0.88–2.5)	No	Age, smoking, family history, physical activity, hormone replacement therapy, NSAIDs, alcohol	Age 25–74 y
Ford (1999), USA	1971–92	M 102 F 117	Subscapular/triceps ratio >1.5 vs <0.6 (5)	0.81 (0.22–3.0) 0.88 (0.17–4.5)	No No	Age, race, education, smoking, cholesterol, physical activity, alcohol	Age 25–74 y
Colorectal adenoma, cohort studies							
Giovannucci *et al.* (1995), USA	1986–92	M 197 M 131	≥0.99 vs <0.90 (5)	0.77 (0.48–1.2) 3.4 (1.6–7.5)	No Yes	Age, screening, family history, smoking, physical activity, NSAIDs, five foods/nutrients, alcohol	Small adenomas Large adenomas
Giovannucci *et al.* (1996), USA	1976–92	F 125 F 330	Highest vs lowest quintile	1.2 (0.65–2.3) 1.4 (0.98–2.1)	No No	Age, family history, screening, smoking, NSAIDs, four foods/ nutrients, alcohol, BMI	Large adenomas All adenomas
Colon cancer, case–control studies							
Caan *et al.* (1998), USA	1991–92	M 927 F 742	Highest vs lowest quintile	1.3 (0.98–1.7) 1.7 (1.2–2.4)	Yes Yes	Age, NSAIDs, energy intake, fibre, calcium, family history, physical activity	Population-based
Russo *et al.* (1998), Italy	1992–96	F 530	>0.90 vs <0.82 (3)	1.6 (1.1–2.1)	Yes	Age, education, physical activity, energy intake	Hospital-based

Table 25 (contd)

Author, date, study location	Study dates	No. of cases	WHR range contrasts (no. of categories)	Relative risk (95% CI)	Trend	Adjustment for confounding	Comments
Rectal cancer, case–control studies							
Russo *et al.* (1998), Italy	1992–96	F 289	≥ 0.9 vs <0.82 (3)	1.6 (1.1–2.4)	Yes	Age, education, physical activity, energy intake	Hospital-based
Colorectal adenoma, case–control studies							
Shinchi *et al.* (1994), Japan	1991–92	M,F 228 M,F 102	≥ 0.96 vs <0.88 (4)	1.5 (0.9–2.5) 2.9 (1.4–5.9)	No Yes	Smoking, alcohol, physical activity	All adenomas Large adenomas Age 49–55 years
Kono *et al.* (1999), Japan	1995–96	M 189	>0.96 vs <0.87 (4)	2.0 (0.9–4.2)	Yes	Smoking, aochol	Age 47–55 years

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories

promotion and progression of adenomas towards cancer. Alternatively, this pattern could appear simply because many other factors can lead small adenomas not to progress, so that among people with small adenomas those other causes dilute the association of obesity with risk.

It is important to note that the strength of the association between colorectal neoplasia and WHR is no greater than the strength of the association with BMI. It is unlikely, therefore, that the association with BMI is simply a proxy for a body fat distribution phenotype such as that indicated by the WHR. BMI is strongly associated, however, with WHR, so it is difficult to be sure that, as measured, the independent effects of each are truly separable in epidemiological studies. In addition, it may be specifically the intra-abdominal fat stores that account for the associations with WHR, and that the crude measure of the total circumferences, which includes both intra-abdominal and subcutaneous fat depots, does not separate those two depots.

In most of the epidemiological studies, body weight (as a measure of obesity) has been obtained by self-reporting. Case–control studies use the weight before onset of symptoms leading to the diagnosis of cancer, as weight loss is a frequent consequence of undiagnosed colorectal cancer. In most of the case–control studies of adenomas, both the cases and controls came from screened populations, so these are truly cross-sectional studies by design. Nonetheless, because adenomas rarely cause weight loss, there should be no bias in the assessment of weight as a risk factor. In prospective studies, current weight at baseline is usually the measure, although some studies have also included retrospective recall of weight from earlier in life (e.g., Lee & Paffenbarger, 1992a; Le Marchand *et al.*, 1992).

Latency can be inferred either by examining lifetime retrospective weight histories or from prospective studies by examining patterns of associations according to the length of follow-up. These analyses of differences in the association between BMI and cancer at different periods in life suggest that the observed association between adult obesity and colorectal neoplasia is probably not due simply to a residual effect from a stronger association earlier in life, nearer to the time of adenoma initiation. In view of the observation that the association with obesity is stronger for larger adenomas, the relationship between BMI-associated factors and cancer most likely follows the pathways of promotional effects on adenoma growth and progression.

In summary, both case–control and cohort studies have shown associations between various measures of adiposity and the risk of colorectal neoplasia. The association is not stronger for adenomas than for cancer, nor is it stronger earlier in life than later in life. The association is stronger, however, for larger adenomas than for smaller ones, and stronger for men than for women. These patterns suggest an effect of factors related to adiposity on the promotion of cancer and a possible counteracting effect on these factors by estrogens.

Breast cancer

The hypothesis that a chronic state of positive energy balance promotes tumour growth has been examined since the early 1930s in animal models as one rationale for the increasing incidence of female breast cancer in developing countries (Tannenbaum, 1945). Epidemiological studies in humans first demonstrated in the 1970s that heavier women were at increased risk of breast cancer (de Waard & Baanders-van Halewijn, 1974; Blitzer *et al.*, 1976). The influence of various measures of body size has been most extensively explored for breast cancer, in part because of the inconsistency in observed associations. The most informative epidemiological studies are those that distinguish between pre- and postmenopausal breast cancer, examine the effect of weight, weight gain and central body fat at various ages and are designed to examine the possible differential effects of exogenous and endogenous estrogens. In view of intriguing evidence obtained in the late 1990s that insulin-related growth factors (IGF) may influence breast cancer risk (see section on Mechanisms later in this Chapter), recent studies have begun to explore possible effects of IGF and body weight (Yu & Rohan, 2000).

Over 100 studies have examined the association of three major anthropometric measures (weight or BMI at different ages, central fat distribution, adult weight gain) and female breast cancer incidence and prognosis, with most studies examining weight or BMI, often at different periods of life. Studies that have examined the association of weight or BMI with cancer at many different sites have limited information on breast cancer incidence, have generally not adjusted for confounding, and therefore are not included in this review. Because of the complexity of the association of the various anthropometric measures with breast cancer and the volume of the literature, only studies with at least 200 cases for either pre- or postmenopausal breast cancer are summarized in Tables 26–28. The information in these tables is organized by premenopausal and postmenopausal breast cancer incidence, with data on cohort and case–control studies summarized under each of these headings. Data are summarized in the table and text for three major anthropometric measures: (1) BMI or relative weight, (2) weight at different ages and adult weight change, and (3) body fat distribution. Findings on breast cancer prognosis and those relating to birth weight and the interaction of weight with age at menarche are briefly summarized in the text but not included in the tables. In general, the many studies conducted have found that taller women are at increased risk for breast cancer

Table 26. Studies of body mass index and risk of breast cancer

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend*	Adjustment for confounding	Comments
Premenopausal breast cancer							
Cohort studies							
Le Marchand *et al.* (1988a), USA	1972–83	289	Tertiles	Age 30–44: 0.78 (0.46–1.3) Age 45–49: 1.1 (0.63–1.8)	No	Age, age at first birth, socioeconomic status	< 50 years, Hawaii
Tretli (1989), Norway	1963–81	3305	RR given for 1 unit increase	0.84 (0.74–0.95)	Yes		< 50 years
Vatten & Kvinnsland (1992), Norway	1974–88	291	≥27 vs 22 (4)	0.78 (0.65–0.94)	Yes	Age, reproductive risk factors, occupation, country of residence	≤ 50 years
Törnberg & Carstensen (1994), Sweden	1963–87	373	≥ 28 vs <22 (5)	0.41	Yes	Age	< 55 years
Huang *et al.* (1997), USA	1976–92	1000	> 31.0 vs ≤20.0 (10)	0.62 (0.45–0.86)	Yes	Age, history of benign breast disease, family history, reproductive factors	Nurses, < 55 years
Case–control studies							
Paffenbarger *et al.* (1980), USA	1970–77	374	≥ 24.5 vs < 21.5 (3)	0.65	No	Age, ethnicity, parity	Hospital-based
Lubin *et al.* (1985), Israel	1975–78	363	Comparison of mean BMI	*p* not signficant	NE	Age, ethnic origin	Hospital-based
Hislop *et al.* (1986), Canada	1980–82	306	≥ 27 vs ≤ 21 (4)	0.84 (0.52–1.4)	No	Age	Population-based
Hsieh *et al.* (1990), international	NS	3993 pre- and post	Normal BMI not defined; obese defined as + 4 kg/m^2	1.0 (0.98–1.1)	No	Age, centre, reproductive factors	Hospital-based
Chu *et al.* (1991), USA	1980–82	2053	Sextiles – cutpoints not stated by menopausal status	1.3 (0.9–2.0)	Yes	Age, reproductive risk factors, family history, surgical biopsy for benign breast disease	Population-based

Table 26 (contd)

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend	Adjustment for confounding	Comments
Brinton & Swanson (1992), USA	1973–80	414	≥26 vs < 20 (5)	0.65 (0.4–1.0)	Yes	Age, age at menarche, education	Population-based, <50 years
Francheschi *et al.* (1996), Italy	1991–94	988	>28.8 vs < 21.7 (5)	0.7 (0.5–0.9)	Yes	Age, centre, education, parity, total energy and alcohol intake	Hospital-based
Swanson *et al.* (1996), USA	1990–92	1588	>28.8 vs <22.0 (4)	0.65 (0.5–0.8)	Yes	Age, centre, ethnicity, reproductive factors, alcohol, oral contraceptive use	Population-based, <45 years
Yong *et al.* (1996), USA	1973–81	226	≥34.7 vs < 26.8 (5)	0.9 (0.6–1.4)	No	Age, education, reproductive risk factors, history of benign breast disease, family history	Population-based
Ziegler *et al.* (1996) Asia	1983–87	421	>31.3 vs <22.9 (6)	1.6 (0.87–2.9)	No	Age, ethnicity, centre, reproductive risk factors, history of benign breast disease, family history	Population-based
Chie *et al.* (1998), Taiwan	1993–94	334	≥25 vs <20 (4)	0.5 (0.2–1.2)	No	Age, education, family history, reproductive factors, oral contraceptive use	Hospital-based
Coates *et al.* (1999), USA	1990–92	1590	>30.4 vs <21.5 (5)	0.69 (0.54–0.88)	Yes	Age, centre, ethnicity, family history, history of breast biopsy, education, reproductive factors, history of mammograms, alcohol, height, oral contraceptive use	Population-based, <44 years
Peacock *et al.* (1999), USA	1983–90	845	≥27.1 vs ≤19.9 (5)	0.67 (0.49–0.91)	Yes	Age, age at menarche	Population-based, <45 years

Table 26 (contd)

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend	Adjustment for confounding	Comments
Enger *et al.* (2000), USA	1983–89	714	≥27.1 vs <21.7 (4)	ER+/PgR+: 1.1 (0.70–1.8) ER+/PgR–: 0.92 (0.34–2.5) ER–/PR–: 1.1 (0.56–1.7) Unknown: 0.80 (0.53–1.2)	No	Age, socioeconomic status, reproductive risk factors, family history, physical activity	Population-based
Hall *et al.* (2000b), USA	1993–96	389	>30.1 vs <24.6 (3)	Black: 0.89 (0.38–2.1) White: 0.46 (0.26–0.80)	No	Age, reproductive risk factors, education	Population-based
Postmenopausal breast cancer							
Cohort studies							
Le Marchand *et al.* (1988a), Hawaii, USA	1972–83	280	Tertiles	Age 50–54: 1.2 (0.70–2.0) Age 55–65: 1.2 (0.74–2.1)	No	Age, age at first birth, socioeconomic status	≥50 years
Tretli (1989), Norway	1963–81	5122	RR given for 1 unit increase	1.2 (1.1–1.2)	Yes		≥50 years
Sellers *et al.* (1992), USA	1986	469	≥30.7 vs ≤ 22.9	No family history : 1.5 (1.1–2.1) Family history: 2.2 (1.4–3.6)	Yes No	Age	≥ 55 years
Tornberg & Carstensen (1994), Sweden	1963–87	1093	≥28 vs <22 (5)	1.1	Yes	Age	≥55 years
Huang *et al.* (1997), USA	1976–92	1517	>31.0 vs ≤20.0 (10)	1.1 (0.87–1.5)	No	Age, history of benign breast disease, family history, reproductive factors	≥55 years
Case-control studies							
Paffenbarger *et al.* (1980), USA	1970–77	1029	≥24.5 vs <21.5 (3)	1.4	Yes	Age, ethnicity, parity	Hospital-based
Lubin *et al.* (1985), Israel	1975–78	664	≥27.1 vs ≤19 (4)	2.5	Yes	Age, ethnic origin, education, reproductive factors, history of benign breast disease, family history	Hospital-based

Table 26 (contd)

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend	Adjustment for confounding	Comments
Hislop *et al.* (1986), Canada	1980–82	517	≥27 vs ≤21 (4)	0.88 (0.59–1.3)	No	Age	Population-based
Kolonel *et al.* (1986) USA	1975–80	272	Weight: highest vs lowest quartile	Japanese: 1.6 (0.8–3.1) White: 1.7 (0.8–3.4)	No	Age, reproductive risk factors, history of benign breast disease, family history	Population-based; Hawaii
Bouchardy *et al.* (1990), France	NS	584	> 27 + vs <23 (3)	Age 55–64: 0.9 Age 65–92: 1.0	Yes	Socioeconomic status reproductive risk factors, prior breast biopsy, family history	Hospital-based, ≥ 55 years
Hsieh *et al.* (1990), Japan	NS	3993 pre- and post-	Normal BMI not defined; obese defined as + 4 kg/m^2	1.1 (1.1–1.2)	No	Age, centre, reproductive factors	Hospital-based
Chu *et al.* (1991), USA	1980–82	547	Sextiles – cutpoints not stated by meno-pausal status	2.7 (1.4–5.4)	Yes	Age, reproductive risk factors, family history, surgical biopsy for benign breast disease	Population-based
Brinton & Swanson (1992), USA	1973–80	1114	≥ 26 vs <20 (5)	0.98 (0.7–1.3)	No	Age, age at menarche, education	Population-based, ≥ 50 years
Harris *et al.* (1992), USA	1987–89	412	> 27 vs <22 (3)	1.5 (1.0–2.3)	Yes	Age, education, parity, family history	Hospital-based
Franceschi *et al.* (1996), Italy	1991–94	1574	>28.8 vs <21.7 (5)	1.4 (1.1–1.8)	Yes	Age, centre, education, parity, total energy and alcohol intake	Hospital-based
Yong *et al.* (1996), USA	1973–81	1198	≥34.7 vs 26.8 (5)	1.3 (1.1–1.6)	Yes	Age, education, reproductive risk factors, history of benign breast disease, family history	Population-based

Table 26 (contd)

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend	Adjustment for confounding	Comments
Chie *et al.* (1998), Taiwan	1993–94	216	≥25 vs < 20 (4)	1.9 (0.5–7.3)	No	Age, education, family history, reproductive factors, oral contraceptive use	Hospital-based
Galanis *et al.* (1998a), USA	1975–94	292	>26 + vs <19.6 (5)	1.5 (1.0–2.3)	Yes	Age, education, ethnicity and drinking status	Population-based, Hawaii, ≥50 years
Magnusson *et al.* (1998), Sweden	1993–95	2904	≥28.3 vs < 22.2 (5)	1.6 (1.4–2.0)	Yes	Age, reproductive factors, use of hormone replacement therapy	Population-based
Enger *et al.* (2000), USA	1987–89	1091	≥27.1 vs <21.7 (4)	ER+/PgR+: 2.4 (1.7–3.5) ER+/PgR–: 1.3 (0.78–2.2) ER–/PgR–: 1.2 (0.70–2.0) Unknown: 1.6 (1.1–2.2)	Yes No No Yes	Age, socioeconomic status, reproductive risk factors, family history, alcohol, physical activity	Population-based
Hall *et al.* (2000b), USA	1993–96	391	>30.1 vs <24.6 (3)	Black: 0.68 (0.33–1.4) White: 1.1 (0.58–2.0)	No	Age, reproductive risk factors, education	Population-based

NE, not estimated
ER, estrogen receptor
PgR, progesterone receptor
* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories

Table 27. Young adult, usual or recent BMI and adult weight change and risk of breast cancer

Author, date, study location	Study dates or date at diagnosis	No. of cases	BMI, Young adult (18–25 y)		BMI, usual or recent adult		Adult weight change		Adjustment for confounding
			BMI range contrasts (no. of categories)	RR (95% CI)	BMI range contrasts (no. of categories)	RR (95% CI)	BMI range contrasts (no. of categories	RR (95% CI)	
Premenopausal breast cancer									
Cohort studies									
Le Marchand *et al.*, (1988a), USA	1972–83	289	NA	NA	Tertiles	0.78 (0.46–1.3), age 30–44 y, 1.1 (0.63–1.8), age 45–49 y	Tertiles	0.67 (0.39–1.2), age 30–44 y 1.1(0.64–1.8), age 45–49 y	Age, age at first birth, socio-economic status
Huang *et al.* (1997), London *et al.* (1989), USA	1976–92	598	≥25 vs <20.0 (5)	0.6 (0.5–0.8), age 18	>31.0 vs ≤20.0 (10)	0.62 (0.45–0.86)	Gain >25 kg vs loss or gain ≤2.0 kg (6)	0.74 (0.54–1.0)	London: Age, height, history of benign breast disease, family history, reproductive factors, smoking Huang: Age, height, history of benign breast disease, family history, reproductive factors Weight gain data adjusted for BMI at age 18 y
Case–control studies									
Paffenbarger *et al.* (1980), USA	1970–77	372	≥22.0 vs <19.0 (3)	0.70, age 20 y	≥24.5 vs ≤21.5 (3)	0.65	NA	NA	Age, ethnicity, parity

Table 27 (contd)

Author, date, study location	Study dates or date at diagnosis	No. of cases	BMI, Young adult (18–25 y)		BMI, usual or recent adult		Adult weight change		Adjustment for confounding (95% CI)
			BMI range contrasts (no. of categories)	RR (95% CI)	BMI range contrasts (no. of categories)	RR (95% CI)	BMI range contrasts (no. of categories	RR	
Chu *et al.* (1991), USA	1980–82	2053	Sextiles – cutpoints not stated by menopausal status	0.6 (0.2–0.9), age 18 y	Sextiles – cutpoints not stated by menopausal status	1.3 (0.9–2.0)	NA	NA	Age, reproductive factors, family history, surgical biopsy for benign breast disease
Brinton & Swanson (1992), USA	1973–80	414	>25 vs <19 (5)	0.58 (0.3–1.1), age 20 y	>26+ vs < 20 (5)	0.65 (0.4–1.0)	Gain 6.0+ BMI vs no change (5)	0.47 (0.3–0.9)	Age, age at menarche, education
Coates *et al.* (1999), USA	1990–92	1590	>22.8 vs <18.5 (5)	0.75 (0.59–0.95), age 20	>30.4 vs <21.5 (5)	0.69 (0.54–0.88)	Gained ≥ 21 kg vs gained or lost ± 2 kg	0.72 (0.54–0.95)	Age, centre,ethnicity, family history, history of breast biopsy, education, reproductive factors, history of mammograms, alcohol, height, oral contraceptive use. Weight gain adjusted for BMI at age 20 y
Peacock *et al.* (1999), USA	1983–90	845	≥27.1 vs ≤19.9 (5)	0.71 (0.53–0.96), age 18 y	≥27.1 vs ≤19.9 (5)	0.67 (0.49–0.91)	Average annual BMI change of ≥0.25 units	0.70 (0.54–0.90)	Age at menarche
Postmenopausal breast cancer									
Cohort studies									
Le Marchand *et al.* (1988a), USA	1972–83	280	NA	NA	Tertiles	1.2 (0.70–2.0), age 50–54 y 1.2 (0.74–2.1), age 55–65 y	Tertiles Change in BMI	Age 50–54 y: 1.1 (0.66–1.8) Age 55–65 y: 2.3 (1.4–3.7)	Age, age at first birth, socio-economic status

Table 27 (contd)

Author, date, study location	Study dates or date at diagnosis	No. of cases	BMI, Young adult ages (18–25 y) BMI range contrasts (no. of categories)	RR (95% CI)	BMI, usual or recent adult BMI range contrasts (no. of categories)	RR (95% CI)	Adult weight change BMI range contrasts (no. of categories	RR	Adjustment for confounding (95% CI)
Folsom *et al.* (1990), Sellers *et al.* (1992), USA	1985–86	382	≥24.6 vs ≤20.0 (5), age 18	Family history –ve: 0.64 (0.45–0.91) Family history +ve: 0.88 (0.46–1.7)	≥30.7 vs ≤22.9 (5)	Family history –ve: 1.5 (1.1–2.1) Family history +ve: 2.2 (1.4–3.6)	Current–weight at age 18 y >17.3 vs <8.2 kg (3)	1.6 (1.1–2.3) (data on 225 women)	Age Weight gain data adjusted for BMI at age 18 y
Huang *et al.* (1997), London *et al.* (1989), USA	1976–92	384	≥25 vs <20.0 (5)	0.8 (0.6–1.2) age 18 y	> 31.0 vs ≤ 20.0 (10)	1.1 (0.87–1.5)	Gain > 25 kg vs loss or gain <2 kg (6)	1.4 (1.1–1.8)	London: Age, height, history of benign breast disease, family history, reproductive factors,smoking Huang: Age, height, history of benign breast disease, family history, reproductive factors Weight gain data adjusted for BMI at age 18
Case–control studies									
Paffenbarger *et al.* (1980), USA	1970–77	991	<19.0 (3)	≥22.0 vs age 20 y	1.0, <21.5 (3)	≥24.5 vs	1.4	NA	NA Age, parity
Chu *et al.* (1991), USA	1980–82	547	Sextiles – cutpoints not stated by meno-pausal status	0.3 (0.03–2.2), age 18 y	Sextiles – cutpoints not stated by menopausal status	2.7 (1.4–5.4)	NA	NA	Age, reproductive factors, family history, surgical biopsy for benign breast disease

Table 27 (contd)

Author, date, study location	Study dates or date at diagnosis	No. of cases	BMI, Young adult (18–25 y)		BMI, usual or recent adult		Adult weight change		Adjustment for confounding
			BMI range contrasts (no. of categories)	RR (95% CI)	BMI range contrasts (no. of categories)	RR (95% CI)	BMI range contrasts (no. of categories	RR (95% CI)	
Brinton & Swanson (1992), USA	1973–80	1107	≥25 vs <19 (5), age 18 y	0.60 (0.4–0.9)	≥26 vs <20 (5)	0.98 (0.7–1.3)	BMI gain 6.0+ vs no change (5)	1.5 (1.1–2.2)	Age, age at menarche, education
Magnusson *et al.* (1998), Sweden	1993–95	2326	≥22.7 vs <18.7 (5)	0.83 (0.69–1.0) age 18 y	≥28.3 vs <22.2 (5)	1.6 (1.4–2.0)	≥30 kg vs <0 kg (5)	1.4 (1.1–1.9)	Age, reproductive factors, use of hormone replacement therapy
Enger *et al.* (2000), USA	1987–89	1091	≥27.1 vs <21.7 (4), age 18	ER+/PgR+: 0.75 (0.38–1.5) ER+/PgR–: 0.53 (0.16–1.8) ER–/PgR–: 0.79 (0.27–2.3) Unknown: 0.77 (0.38–1.6)	≥27.1 vs <21.7 (4)	ER+/PgR+: 2.4 (1.7–3.5) ER+/PgR–: 1.3 (0.78–2.2) ER–/PR–: 1.2 (0.70–2.0) Unknown: 1.6 (1.1–2.2)	% change age 18 to reference age, >29.2 vs ≤0 (4)	ER+/PgR+: 2.3 (1.6–3.4) ER+/PgR–: 0.99 (0.58–1.8) ER–/PR–: 1.8 (0.91–3.4) Unknown: 1.7 (1.2–2.5)	Age, socio-economic status reproductive risk factors, family history, alcohol, physical activity

NA, not analysed
ER, estrogen receptor
PgR, progesterone receptor

Table 28. Studies of body fat distribution and risk of breast cancer

Author, date, study location	Study dates	No. of cases	WHR range contrasts (no. of categories)	Relative risk (95% CI)	Trend*	Adjustment for confounding	Comments
Premenopausal breast cancer							
Cohort studies							
Kaaks *et al.* (1998), Netherlands	1984–96	147	WHR: >0.80 vs ≤0.73 (4) Waist: >83.5 cm vs ≤71 cm (4)	WHR: 0.96 (0.60–1.5) Waist: 0.92 (0.57–1.5)	WHR: No Waist: No	Age, reproductive factors, height, weight	Breast cancer screening
Huang *et al.* (1999), USA	1976–94	197	WHR: ≥0.84 vs <0.73 (5) Waist: ≥36.0 vs <27.9 (5)	WHR: 1.4 (0.86–2.4) Waist: 1.7 (0.74–4.1)	WHR: No Waist: No	Age, BMI	Nurses
Case–control studies							
Franceschi *et al.* (1996), Italy	1991–94	947	> 0.88 vs < 0.78 (5)	0.7 (0.5–1.0)	No	Age, BMI, centre, education, parity, total energy and alcohol intake	Hospital-based
Swanson *et al.* (1996), USA	1990–92	1588	>0.858 vs 0.753 (4)	0.95 (0.8–1.2)	No	Age, BMI, centre, reproductive factors, oral contraceptive use, alcohol	Population-based, < 45 years
Hall *et al.* (2000b), USA	1993–96	370	> 0.86 vs <0.77 (3)	Black: 2.5 (1.1–5.7) White: 2.4 (1.2–5.1)	Yes	Age, BMI, reproductive factors, education	Population-based
Postmenopausal breast cancer							
Cohort studies							
Sellers *et al.* (1992), USA	1986	465	> 0.91 vs < 0.76 (5)	No family history 1.2 (0.87–1.7) Family history 3.2 (2.1–5.0)	No	Age	> 55 years
Huang *et al.* (1999), USA	1976–94	840	WHR: >0.84 vs <0.73 (5) Waist: >36.0 vs <27.9 (5)	WHR: 1.2 (0.96–1.6) Waist: 1.3 (0.88–1.8)	WHR: Yes Waist: No	Age, BMI	Nurses

Table 28 (contd)

Author, date, study location	Study dates	No. of cases	WHR range contrasts (no. of categories)	Relative risk (95% CI)	Trend	Adjustment for confounding	Comments
Case–control studies							
Franceschi *et al.* (1996), Italy	1991–94	1441	> 0.88 vs < 0.78 (5)	1.0 (0.8–1.3)	No	Age, BMI, centre, education, parity, total energy and alcohol intake	Hospital-based
Hall *et al.* (2000b) USA	1993–96	380	> 0.86 vs < 0.77 (3)	Black: 1.6 (0.70–3.8) White: 1.6 (0.88–3.1)	No	Age, BMI, reproductive risk factors, education	Population-based

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories
WHR, waist/hip ratio

irrespective of menopausal status, while height has generally not been related to breast cancer prognosis, but data on height are not included in this review.

Premenopausal breast cancer

BMI or relative weight

Cohort studies

Cohort and nested case–control studies within cohorts are fairly few, but in general have found greater reductions in premenopausal breast cancer risk than case–control studies (Table 26). Estimates of 0.41 to 0.9 (Willett *et al.*, 1985; London *et al.*, 1989; Swanson *et al.*, 1989; Tretli, 1989; Vatten & Kvinnsland, 1992; Törnberg & Carstensen, 1994; Huang *et al.*, 1997) have been reported for recent or usual BMI greater than 27 to 28 kg/m^2. The studies of Willett, London, and Huang are all derived from the Nurses' Health Study and reflect longer periods of follow-up and more cancer cases in each subsequent study. Two early studies suggested that the protective effect among heavier women was limited to early-stage disease due to poorer detection of small tumours (Willett *et al.*, 1985; Swanson *et al.*, 1989). However, more recent studies including case–control (see below) and cohort studies presented in this chapter suggest that detection bias could not explain the increased risk for breast cancer observed among lean premenopausal women (London *et al.*, 1989; Brinton & Swanson, 1992). Some of the most precise estimates of risk derive from the Nurses' Health Study (Willett *et al.*, 1985; London *et al.*, 1989; Huang *et al.*, 1997). In an analysis from the 1992 follow-up of that cohort, the risk estimate for the top decile of recent BMI (>31.0 kg/m^2) was 0.62. Relative risk estimates for the 2nd to 7th deciles were essentially null and then decreased to 0.86 and 0.80 for the 8th and 9th deciles, respectively, suggesting that the protective effect was limited to very high BMI. Questions have been raised about the selective nature of the study population (all nurses) within the Nurses' Health Study. One other large, well designed population-based Norwegian cohort study provided risk estimates that are perhaps more generalizable to a population of white women (Tretli, 1989). In that cohort, relative risk estimates for stage I breast cancer for women in the top quintile compared with the bottom quintile of BMI were 0.80, 0.54, 0.54 and 0.63 for women aged 30–34, 35–39, 40–44 and 45–49 years. Relative risk estimates for stage II–IV breast cancer were 1.2, 1.2, 0.97 and 1.4, respectively, for the same five-year age groups. However, the only statistically significant relative risks were those for stage I breast cancer among women 35–49 years.

Case–control studies

Heavier women have been found to have a decreased risk of premenopausal breast cancer in most case–control studies (Paffenbarger *et al.*, 1980; Hislop *et al.*, 1986; Brinton & Swanson, 1992; Franceschi *et al.*, 1996, Swanson *et al.*, 1996; Chie *et al.*, 1998; Coates *et al.*, 1999; Peacock *et al.*, 1999). Risk estimates of 0.6 to 0.8 have generally been reported for the highest compared with the lowest BMI or weight groups. A limited number of case–control studies showed no association or a non-significant positive one (Hsieh *et al.*, 1990; Chu *et al.*, 1991; Ziegler *et al.*, 1996, Enger *et al.*, 2000; Hall *et al.*, 2000b). Two case–control studies have confirmed the findings in cohort studies that detection bias does not explain the increased risk for breast cancer observed among lean premenopausal women (Swanson *et al.*, 1996; Coates *et al.*, 1999). This risk may be modified by height. An informative large case–control study that allowed stratified analysis of the effects of both height and weight found that risk was increased about twofold among women who were tall and thin compared with women who were heavy and short (Swanson *et al.*, 1996).

Weight change and young adult weight

Data on weight change, young adult weight and premenopausal breast cancer are limited but generally show similar inverse associations irrespective of study design.

Cohort studies

Consistent with findings for recent BMI and premenopausal breast cancer, two cohort studies have reported that weight gain is associated with reduced risk of premenopausal breast cancer (Le Marchand *et al.*, 1988a; Huang *et al.*, 1997). As shown in Table 27, an analysis within the large Nurses' Health Study gave a risk estimate of 0.74 (95% CI 0.54–1.0) for the top sextile of weight gain (>25 kg) from age 18 years (Huang *et al.*, 1997). Heavier weight or BMI during young adulthood, generally reported for ages 18–20 years, was associated with a 25–40% decrease in breast cancer in the limited number of cohort studies in which it has been examined (Le Marchand *et al.*, 1988a; London *et al.*, 1989). In a large US cohort, the risk estimate for the 5th compared with the 1st quintile of BMI at age 18 years was identical to that for recent BMI (London *et al.*, 1989).

Case–control studies

In the limited number of case–control studies (Brinton & Swanson, 1992; Coates *et al.*, 1999; Peacock *et al.*, 1999), weight gain was associated with a 30% reduction in risk (Table 27). The largest case–control study that examined weight gain of 1590 women in the USA found a reduced relative risk of 0.72 (95% CI 0.54–0.95) with weight gain of 21 kg or greater. In case–control studies, heavier weight or BMI during young adulthood, generally reported as ages 18–20 years, was associated with a 25–40% decrease in breast cancer (Paffenbarger *et al.*, 1980; Chu *et al.*, 1991; Brinton & Swanson, 1992; Coates *et al.*, 1999; Peacock *et al.*, 1999). This

inverse association with young adult weight or weight gain was seen even in the absence of an inverse association between recent BMI and breast cancer (Chu *et al.*, 1991).

Central adiposity

Data on central adiposity and premenopausal breast cancer risk are inconsistent but the most informative studies suggest that neither waist nor waist to hip ratio (WHR) is related to premenopausal breast cancer risk (Swanson *et al.*, 1996; Kaaks *et al.*, 1998).

Cohort studies

One study found no association between waist or WHR (Kaaks *et al.*, 1998), one showed a modest non-significant increase in risk with WHR (Huang *et al.*, 1999) and one reported a statistically significant increase in risk with WHR (Sonnenschein *et al.*, 1999) (Table 28). A later follow-up, with more cases, of a cohort that first found a positive association (den Tonkelaar *et al.*, 1995a) did not detect any association between WHR and breast cancer incidence (Kaaks *et al.*, 1998).

Case–control studies

Two studies found no association between various measures of central adiposity (Petrek *et al.*, 1993; Swanson *et al.*, 1996), one found a non-significant decrease in risk (Franceschi *et al.*, 1996), one found modest non-significantly increased risk (Hall *et al.*, 2000b) and two reported statistically significant increases in risk with WHR (Männistö *et al.*, 1996; Ng *et al.*, 1997) (Table 28). A multi-centre population-based case–control study in the USA was particularly informative in terms of having a large number of premenopausal breast cancer cases and measured waist and hip circumferences (Swanson *et al.*, 1996), and found no association of WHR with breast cancer risk.

Postmenopausal breast cancer

BMI or relative weight

In contrast to the evidence on premenopausal breast cancer, heavier women have been found to be at increased risk of postmenopausal breast cancer in most studies (Table 26).

Cohort studies

Findings from a number of prospective cohort studies indicate a modest increased risk associated with recent BMI (Le Marchand *et al.*, 1988a; Tretli, 1989; Sellers *et al.*, 1992; Törnberg & Carstensen, 1994; Huang *et al.*, 1997). Other known risk factors that are likely to confound the association of weight with breast cancer include exogenous estrogen use and family history of breast cancer, and few studies have performed stratified analyses to explore the discrete effects of such factors. One of the largest cohort studies found no increase in risk (RR = 1.1; 95% CI 0.87–1.5) for all women (Huang *et al.*, 1997). However, among women who had not used hormone replacement therapy, risk was increased to 1.6. In another large cohort, heavier women with a family history of breast cancer had a greater risk of developing breast cancer than heavier women without a family history (Sellers *et al.*, 1992).

The Pooling Project included data from eight prospective cohorts (one each in Canada, the Netherlands and Sweden and five in the USA) comprising 337 819 women and 4385 incident invasive breast cancer cases. Risk of breast cancer increased above a BMI of 20 kg/m^2 up to a relative risk of 1.3 (95% CI 1.1–1.5) for women with BMI over 28 kg/m^2, and did not increase further. This analysis also found that the association between BMI and breast cancer was stronger and more significant among women who had never used postmenopausal hormone replacement therapy. In a subgroup analysis from the Oxford Pooling Project, which combined data on 50 cohorts primarily to examine the effect of estrogen replacement therapy (ERT) and breast cancer risk, among women who had recently used ERT for more than five years, the relative risk in those with a BMI over 25 kg/m^2 was 1.5 and was null among those with a BMI less than 25 kg/m^2 (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). These risk estimates were not adjusted for duration of ERT. The results of these two analyses confirm the earlier finding of an significant interaction between body mass and hormone replacement therapy from the Nurses' Health Study (Huang *et al.*, 1997). The stronger association among non-users of hormone replacement therapy provides strong support for the hypothesis that the mechanism for increased risk is largely due to increases in endogenous estrogen production among heavier women.

Case–control studies

Women with BMI above 27–28 kg/m^2 have been reported to be at 10–60% increased risk of breast cancer in many case–control studies (Paffenbarger *et al.*, 1980; Kolonel *et al.*, 1986; Hsieh *et al.*, 1990; Harris *et al.*, 1992; Franceschi *et al.*, 1996; Yong *et al.*, 1996; Galanis *et al.*, 1998a; Magnusson *et al.*, 1998), at a more than twofold increased risk in some others (Lubin *et al.*, 1985; Chu *et al.*, 1991; Chie *et al.*, 1998; Enger *et al.*, 2000) and at no increased risk in a few studies (Hislop *et al.*, 1986, Bouchardy *et al.*, 1990; Brinton & Swanson, 1992; Hall *et al.*, 2000b). However, where examined, risk appeared to increase with age at diagnosis, from 1.1–1.3 among women younger than 60 years to 1.6–2.9 among women older than 65 or 70 years (Franceschi *et al.*, 1996; Yong *et al.*, 1996; La Vecchia *et al.*, 1997a). Only one study has examined breast cancer incidence by estrogen (ER) or progesterone receptor (PgR) status of the tumour (Enger *et al.*, 2000). Risk was 2.4 for a BMI over 27 kg/m^2 among women with ER- and PgR-positive tumours and

was not increased among those with ER- or PgR-negative tumours or with ER-positive but PgR-negative tumours. In the same study, risk associated with BMI did not vary according to ER or PgR status among premenopausal women.

Weight change and young adult weight

At present, the most consistent body-size predictor of postmenopausal breast cancer risk is adult weight gain (Table 27).

Cohort studies

An association of postmenopausal breast cancer risk with adult weight gain has been found in cohort studies (Le Marchand *et al.*, 1988a; Ballard-Barbash *et al.*, 1990a; Folsom *et al.*, 1990; Huang *et al.*, 1997), including those that found no association between BMI at baseline and subsequent development of breast cancer and also adjusted weight gain for baseline BMI (Ballard-Barbash *et al.*, 1990a; Folsom *et al.*, 1990; Huang *et al.*, 1997). Findings from one of the largest cohort studies suggest that the doubling of risk associated with a weight gain of over 20 kg from age 18 years was limited to women who had never used postmenopausal hormone replacement therapy (Huang *et al.*, 1997). The data from this study can be examined to determine if there is a specific level of weight gain at which risk increases. A 20% increase in risk was observed for weight gains between 2 to 20 kg, although this was not statistically significant, while a statistically significant increase in risk of 40% was seen for weight gains of over 20 kg.

In two cohort studies, greater weight or BMI during young adulthood, generally reported for ages 18–20 years, was associated with a 20–30% decrease in breast cancer risk (London *et al.*, 1989; Sellers *et al.*, 1992).

Case–control studies

Weight gain is also a consistent predictor of increased risk in case–control studies (Brinton & Swanson, 1992; Ziegler *et al.*, 1996; Magnusson *et al.*, 1998; Enger *et al.*, 2000). Two case–control studies also examined the effect of BMI or weight gain and hormone replacement therapy and reported similar results. In these studies, modest or no increase in breast cancer risk with increases in BMI was seen, but increases were larger among women not using hormone replacement therapy (Harris *et al.*, 1992; Magnusson *et al.*, 1998). In a large case–control study for which data were not presented in detail, it was noted that the association between weight gain and postmenopausal breast cancer risk was attenuated among current hormone users, although the test for interaction was not statistically significant (Trentham-Dietz *et al.*, 2000).

Greater weight or BMI during young adulthood, generally reported for ages 18–20 years, was associated with a 10–30% decrease in breast cancer risk in most case–control studies (Brinton & Swanson, 1992; Magnusson *et al.*, 1998; Enger *et al.*, 2000) but not in all (Paffenbarger *et al.*, 1980; Trentham-Dietz *et al.*, 2000). A few studies reported on a relative weight measure (Hislop *et al.*, 1986; Brinton & Swanson, 1992) and generally found that lower body weight or size relative to peers at young ages was associated with either no difference or a reduced risk of breast cancer. During the middle decades of life, the risk associated with BMI remains inverse for premenopausal breast cancer, though it shifts from a protective effect to null as women approach the menopause, and increases with age for postmenopausal breast cancer.

Central adiposity

Cohort studies

Increases in central adiposity have been associated with higher breast cancer risk among postmenopausal women in cohort studies (Ballard-Barbash *et al.*, 1990b; Folsom *et al.*, 1990; Sellers *et al.*, 1992; Kaaks *et al.*, 1998),(Table 28) particularly when possible differences in risk related to use of hormone replacement therapy were examined (Huang *et al.*, 1999). Some of these studies adjusted for baseline BMI and, therefore, the risk estimates suggest an independent effect of central adiposity. In the largest cohort study, risk increased from 1.2 among women overall to 1.9 among women who had never used postmenopausal hormone replacement therapy (Huang *et al.*, 1999). Family history of breast and ovarian cancer may modify the observed association in postmenopausal women. In a cohort of postmenopausal women, among women with elevated WHR, only those with a positive family history of breast cancer were at increased risk, while the combination of high WHR with a family history of breast and ovarian cancer was associated with a more than fourfold increase in risk of breast cancer (Sellers *et al.*, 1992). In another large US cohort, risk associated with waist circumference and WHR appeared to vary slightly with family history of breast cancer (Huang *et al.*, 1999). Among women having a family history of breast cancer, risk estimates for the 5th compared to the 1st quintile were 1.2 for waist and 0.73 for WHR. Conversely, amon women without a family history, risk estimates were 1.4 for waist and for WHR.

Case–control studies

Case–control studies have yielded less consistent results. Risk was significantly increased by about double in most studies (Bruning *et al.*, 1992a; Männistö *et al.*, 1996; Ng *et al.*, 1997), non-significantly increased by 60% in one (Hall *et al.*, 2000b) and not increased in some (Petrek *et al.*, 1993; Franceschi *et al.*, 1996). The majority of the studies finding a positive association adjusted for current BMI (Bruning *et al.*, 1992a; Männistö *et al.*, 1996; Ng *et al.*, 1997) and still found an independent effect of central adiposity. However, the largest case–control study found no increase in risk

with higher WHR after adjustment for recent BMI (Franceschi *et al.*, 1996).

Birth weight

Data on birth weight and breast cancer are sparse, somewhat inconsistent, but are accumulating rapidly and suggest a positive association for premenopausal breast cancer. However, most studies on birth weight and breast cancer risk are limited by a very small number of cases, with many having fewer than 100 cases and several less than 50 cases.

Cohort studies

One cohort study has suggested that the effect of birth weight may be modified by childhood height. Among premenopausal women, risk was not significantly increased (RR = 1.2; 95% CI 0.31–4.9) for a birth weight of 3500 g or greater and a height of less than 1.22 m at age seven years, compared with a much higher risk (RR = 5.9; 95% CI 2.0–17.4) for the same birth weight but height greater than 1.22 m at age seven years (De Stavola *et al.*, 2000).

Case–control studies

Two case–control studies found no association between birth weight and breast cancer (Le Marchand *et al.*, 1988b; Ekbom *et al.*, 1997); the 1997 report by Ekbom is an update of an earlier study with a more limited number of cases that did report a positive association (Ekbom *et al.*, 1992). However, more studies reported a positive association, with one case–control study of premenopausal cases under age 37 years showing an increased risk with birth weight over 4500 g (Innes *et al.*, 2000) and other studies finding an increase in risk with increasing birth weight for premenopausal but not postmenopausal breast cancer (Berstein, 1988; Michels *et al.*, 1996; Sanderson *et al.*, 1996) or stronger increases in risk for premenopausal than for postmenopausal breast cancer (De Stavola *et al.*, 2000; Kaijser *et al.*, 2001). Most of these studies suggested that risk increased above a birth weight of 3500 g.

Weight and age at menarche

Age at menarche, an established risk factor for breast cancer, provides an indirect indicator of energy balance during childhood. Nutritional factors, in particular energy balance, appear to be the major determinants of age at menarche. In prospective studies among young girls, the major predictors of age at menarche were weight, height and body fatness (Meyer *et al.*, 1990; Maclure *et al.*, 1991; Merzenich *et al.*, 1993; Koprowski *et al.*, 1999). Early onset of menstrual cycles exposes the breast to ovarian hormones at a younger age and for a longer duration over a lifetime. The potential for energy balance to influence breast cancer risk through age at menarche is greater than might be appreciated by examining the distribution of this variable in developed countries. Although the average age at menarche in these countries is now 12–13 years, in rural China the typical age has been 17–18 years (Chen *et al.*, 1990), similar to that in the developed countries some 200 years ago.

Data from different ethnic populations

As is clear from Tables 26–28, the majority of studies on weight and breast cancer risk have been conducted in European and North American populations. With the exception of studies in Asian or Asian American women (Kolonel *et al.*, 1986; Tao *et al.*, 1988; Kyogoku *et al.*, 1990; Wang *et al.*, 1992; Chie *et al.*, 1996; Ziegler *et al.*, 1996; Ng *et al.*, 1997; Galanis *et al.*, 1998a; Tung *et al.*, 1999) and a single study including stratified results for African American women (Hall *et al.*, 2000b), data on specific non-white populations are limited. Generally, the results in these studies are similar to those reported for white women or from population-based studies that included women from diverse ethnic backgrounds but did not report specific ethnic comparisons within their samples. For example, in a large case–control study (Hall *et al.*, 2000b), risk in African Americans was similar to that in white women for both premenopausal and postmenopausal women for both BMI and WHR. However, in this study, BMI was not related to risk for postmenopausal breast cancer (Table 26). Two smaller studies in China and Japan are not summarized in the tables, but the results were similar to those in other populations. In a small case–control study of 130 cases (menopausal status not stated) in Singapore, risk was markedly increased to 6.1 (95% CI 2.7–14.2) among women with a WHR greater than 0.86, while the risk associated with a BMI greater than 27.5 kg/m^2 was non-significantly elevated (1.2; 95% CI 0.7–2.3) (Ng *et al.*, 1997). In a case–control study of 190 premeno-pausal breast cancer cases and 186 postmenopausal breast cancer cases in Japan, BMI was not associated with premenopausal breast cancer (RR = 0.98; 95% CI 0.46–2.1, for BMI ≥25.1 kg/m^2) and was positively associated with postmenopausal breast cancer (RR = 1.9; 95% CI 1.1–3.2, for BMI ≥25.1 kg/m^2) (Tung *et al.*, 1999).

In a comparison of the effect of body size in various populations, seven countries were separated into those with low (Japan, Taiwan), moderate (Brazil, Greece, Yugoslavia) and high (USA, Wales) risk (Pathak & Whittemore, 1992). At a BMI of 24 kg/m^2, rates of breast cancer increased among postmenopausal women across all countries, with the greatest increases in risk at higher BMI among low- and moderate-risk countries, suggesting that increases in BMI now being observed in those countries (see Chapter 1) may be a major factor contributing to increases in breast cancer rates in countries that previously had low to moderates rates (Hodge *et al.*, 1995, 1996). Further, while risk ratios levelled off at higher BMIs in high-risk countries, this was not the

case in low- to moderate-risk countries, where risk continued to increase exponentially across the full range of body weight.

Intentional weight control or loss

Data on an association between weight loss and breast cancer risk are limited. Four observational epidemiological studies that presented data on weight loss and breast cancer found no statistically significant association (Ballard-Barbash *et al.*, 1990a; Brinton & Swanson, 1992; Ziegler *et al.*, 1996; Huang *et al.*, 1997). In three studies, weight loss occurring over a long interval was associated with a non-significant slight reduced risk (Ballard-Barbash *et al.*, 1990a; Brinton & Swanson, 1992; Trentham-Dietz *et al.*, 1997, 2000). In another, weight loss in the decade before diagnosis was associated with a non-significant decreased risk (Ziegler *et al.*, 1996). One study of premenopausal women found a statistically significant decreased risk (RR = 0.64; 95% CI 0.42–0.98) with weight loss from age 20 years to interview (age 20–44 years) that was present only among cases with low-grade tumours (Coates *et al.*, 1999). One study of postmenopausal women found a statistically significant decreased risk (OR = 0.76; 95% CI 0.61–0.96) with weight loss from age 18 years to interview (age 50–74 years) (Magnusson *et al.*, 1998). These data suggest that weight loss may be beneficial, but are difficult to interpret as the cause of weight loss was not specified.

Breast cancer prognosis

BMI or relative weight

The association of BMI or weight with breast cancer prognosis has been examined in over 50 studies; all of which were cohort in design in terms of evaluating recurrence or death. Nearly all evaluated the effect of BMI at the time of diagnosis on breast cancer prognosis. Heavier women experienced poorer survival and increased likelihood of recurrence in most studies irrespective of menopausal status and after adjustment for stage and treatment (Greenberg *et al.*, 1985; McNee *et al.*, 1987; Hebert *et al.*, 1988; Mohle-Boetani *et al.*, 1988; Lees *et al.*, 1989; Verreault *et al.*, 1989; Coates *et al.*, 1990; Kyogoku *et al.*, 1990; Tretli *et al.*, 1990; Vatten *et al.*, 1991; Senie *et al.*, 1992; Giuffrida *et al.*, 1992; Bastarrachea *et al.*, 1994; Zhang *et al.*, 1995; den Tonkelaar *et al.*, 1995b; Maehle & Tretli, 1996). In several studies, the association with prognosis was limited to or more pronounced among women with stage I and II disease (Verreault *et al.*, 1989; Tretli *et al.*, 1990), estrogen receptor (ER) and progesterone (PgR)-positive status (Coates *et al.*, 1990; Giuffrida *et al.*, 1992; Maehle & Tretli, 1996) and negative nodes (Mohle-Boetani *et al.*, 1988; Newman *et al.*, 1997). While many of the studies have used hospital-based samples of women, the most precise risk estimates are derived from large population-based cohorts of breast cancer cases. In the largest cohort of over 8000 women with breast cancer, risk varied by stage at diagnosis. Among women with stage I disease, women in the upper quintile of BMI had a 70% increased risk of dying from breast cancer; among women with stage II disease, women in the upper quintile had a 40% increased risk. BMI was not associated with risk among women with late stage III and stage IV disease (Tretli *et al.*, 1990). In a subset of 1238 women of this cohort with unilateral breast cancer treated with modified radical mastectomy and followed for 15 years, the risk of dying from breast cancer relative to BMI varied markedly by hormone receptor status (Maehle & Tretli, 1996). Although women with ER- and PgR-positive tumours had nearly a 50% reduced risk of dying from breast cancer, the risk within hormone receptor-positive and -negative groups varied with BMI. Among women with hormone receptor-positive tumours, obese women had a risk of death three times higher than thin women. In contrast, among women with hormone receptor-negative tumours, thin women had a risk of death six times higher than obese women, even after adjustment for lymph node status, tumour diameter and mean nuclear area.

Weight gain

Weight gain is reported in the majority of women undergoing adjuvant therapy for breast cancer (Heasman *et al.*, 1985; Goodwin *et al.*, 1988; Camoriano *et al.*, 1990; Demark-Wahnefried *et al.*, 1993, 1997). Weight gain associated with treatment is lowest among women not receiving systemic therapy, intermediate among women receiving combination therapy and more pronounced among women receiving prednisone and ovarian ablation in addition to adjuvant chemotherapy. Recent research has begun to examine whether changes in energy intake and expenditure during treatment are associated with weight gain, in order to develop interventions to prevent weight gain during treatment (Demark-Wahnefried *et al.*, 1993). Although data on the association of post-diagnosis weight gain and prognosis are limited, the largest study of 391 premenopausal women found that women who gained more than 5.9 kg were 1.5 times more likely to relapse and 1.6 times more likely to die than women who gained less weight (Camoriano *et al.*, 1990).

Body fat distribution

Data on fat distribution and breast cancer prognosis are limited to one study of 119 postmenopausal women with breast cancer that found no association with two measures of skinfold thickness, subscapular and triceps (den Tonkelaar *et al.*, 1995b). No study has examined prognosis in relation to waist or hip circumference.

Conclusion

In populations with a high incidence of breast cancer, the overall association of BMI with premenopausal breast cancer

risk is inverse. This has been found in many cohort and case–control studies that carefully controlled for numerous reproductive and lifestyle factors. The reduction in risk of 0.6 to 0.7 is modest and does not appear to be observed below a BMI of 28 kg/m^2. In contrast to the consistency in the positive association of BMI for postmenopausal breast cancer in terms of both incidence and mortality or prognosis, mortality for premenopausal breast cancer is not lower among heavier women. This may relate to the observation that tumours have tended to be diagnosed at more advanced stages among overweight women. The results are largely from studies performed before mammographic screening was widespread, but are still relevant for young women, as mammographic screening does not begin until ages of 40 to 50 years in most countries. However, in moderate- and low-risk countries, risk of premenopausal breast cancer does not appear to decrease with increasing BMI, which may be due in part to a low prevalence of overweight in such populations.

More than 100 studies conducted during some 30 years in populations in many countries have established that higher body weight is associated with increased breast cancer risk among postmenopausal women. The large majority of cohort and case–control studies have seen positive associations, although the increase in risk with BMI has been somewhat modest. Nearly all of these studies have controlled for a wide variety of reproductive and lifestyle risk factors without altering this positive association. More recent studies have also adjusted for physical activity and still found an association. Risk appears to increase in a stepwise fashion with age.

Adult weight gain has been shown to be a strong and consistent predictor of postmenopausal breast cancer risk. Again, the association was particularly strong among women who were never users of hormone replacement therapy. As with the studies on BMI and breast cancer, adjustment for many breast cancer risk factors, including physical activity, did not weaken these associations.

Endometrial cancer

There is convincing evidence from both cohort studies and case–control studies that adult obesity is associated with a two- to threefold increased risk of endo-metrial cancer (Table 29). Only studies with at least 100 cases are reviewed here, apart from some smaller studies conducted in less-studied populations.

Cohort studies

Cohort studies conducted in various developed countries, including the USA (Lew & Garfinkel, 1979; Le Marchand *et al.*, 1991a), Denmark (Ewertz *et al.*, 1984; Møller *et al.*, 1994), Norway (Tretli & Magnus, 1990) and Sweden (Törnberg & Carstensen, 1994; Terry *et al.*, 1999), have consistently found a direct association between endometrial cancer risk and adult weight or BMI. Only one of these studies adjusted risk estimates for reproductive risk factors (Le Marchand *et al.*, 1991a). In this study, in Hawaii, USA, using historically-recorded weight and height data, the association between adult weight and endometrial cancer was not explained by parity and age at first birth; the association was strongest in older women (over 60 years).

Case–control studies

Consistently with the cohort studies, the great majority of case–control studies have reported an increased risk of endometrial cancer with higher weight (Wynder *et al.*, 1966; Elwood *et al.*, 1977; Kelsey *et al.*, 1982; Henderson *et al.*, 1983; La Vecchia *et al.*, 1984, 1991; Lawrence *et al.*, 1987; Austin *et al.*, 1991; Shu *et al.*, 1991, 1992; Brinton *et al.*, 1992; Swanson *et al.*, 1993; Inoue *et al.*, 1994; Olson *et al.*, 1995; Goodman *et al.*, 1997; Shoff & Newcomb, 1998; Weiderpass *et al.*, 2000). A particularly large and well conducted case–control study with 405 cases and 297 controls (Swanson *et al.*, 1993) reported a two-fold increase in endometrial cancer risk (95% CI 1.2–3.3) among women with BMI >30 kg/m^2 compared with those having BMI <23 kg/m^2. This association was observed in studies conducted in North America, northern Europe, southern Europe and China. Only two (Koumantaki *et al.*, 1989; Parslov *et al.*, 2000) out of 17 case–control studies (18 publications) found no association and none found an inverse association. In most studies, the association between body weight and endometrial cancer was independent of other known risk factors for the disease, such as age, parity, menopausal status, smoking, estrogen replacement therapy and socioeconomic status.

Discussion

A linear increase in risk with increasing weight or BMI has been observed in most studies (Elwood *et al.*, 1977; Kelsey *et al.*, 1982; Henderson *et al.*, 1983; Ewertz *et al.*, 1984; La Vecchia *et al.*, 1984, 1991; Lawrence *et al.*, 1987; Tretli & Magnus, 1990; Austin *et al.*, 1991; Le Marchand *et al.*, 1991a; Brinton *et al.*, 1992; Törnberg & Carstensen, 1994; Olson *et al.*, 1995; Goodman *et al.*, 1997; Terry *et al.*, 1999), However, in other studies, the increased risk was present only for the highest category of body mass (Shu *et al.*, 1991; Swanson *et al.*, 1993; Inoue *et al.*, 1994; Weiderpass *et al.*, 2000). Thus, it is unclear whether the risk of endometrial cancer is elevated only in overweight and obese women or whether the association is also present at lower levels of body weight. This inconsistency in the shape of the relationship across studies may be due to misclassification resulting from the use of weight or BMI as a measure of obesity (see below), to random variation or to true differences between populations.

Table 29. Studies of body mass index and risk of endometrial cancer

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend*	Adjustment for confounding	Comments
Cohort studies							
Lew & Garfinkel (1979), USA	1959–72	NR	40% > average weight	5.4	Yes	Age	Mortality study
Ewertz *et al.* (1984), Denmark	1943–77	115	> 31 vs < 22 (5)	2.3 (0.9–6.2)	Yes	Age	Cancer registry
Tretli & Magnus (1990), Norway	1963–81	2208	Highest vs lowest quartile	2.1 (1.9–2.5)	NE	Age	Tuberculosis screening programme
Le Marchand *et al.* (1991a), USA	1972	214	Weight: highest vs lowest tertile	2.3 (1.0–5.0)	Yes	Age, reproductive factors, socioeconomic status	Age > 60 years
Møller *et al.* (1994), Denmark	1977–87	114	Incidence relative to population	2.0 (1.6–2.4)	NE	Age, calendar period	Cohort of obese women
Törnberg & Carstensen (1994), Sweden	1963–87	412	≥ 28 vs < 22 (5)	2.6	Yes	Age, period of follow-up	Cancer registry
Terry *et al.* (1999), Sweden	1967–92	133	Weight: highest vs lowest quartile	2.4 (1.4–3.8)	Yes	Age	Twin registry
Case–control studies							
Wynder *et al.* (1966), USA	1959–63	112	Weight	Direct association	NE	Age	Hospital-based
Elwood *et al.* (1977), USA	1965–69	212	> 28 vs < 22 (4)	1.9	Yes	Age	Population-based
Kelsey *et al.* (1982), USA	1977–79	167	Weight ≥ 166 lb vs ≤ 125 lb (4)	2.3	Yes	Age, estrogen use, diabetes	Hospital-based
Henderson *et al.* (1983), USA	1972–79	110	Weight ≥ 190 lb vs ≤ 129 lb (5)	17.7	Yes	Age	Population-based
La Vecchia *et al.* (1984), Italy	1979–83	283	≥ 30 vs < 20 (4)	7.6 (4.2–14.0)	Yes	Age	Hospital-based
Lawrence *et al.* (1987), USA	1979–81	200	Weight ≥ 190 lb vs < 140 lb (4)	5.7	Yes	Age	Population-based Non-smokers

Table 29 (contd)

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend	Adjustment for confounding	Comments
Koumantaki *et al.* (1989), Greece	1984	83	Weight per 5 kg	1.0 (0.93–1.1)	NE	Age, reproductive factors estrogen use, smoking	Hospital-based
Austin *et al.* (1991), USA	1985–88	168	> 36.4 ≤ 28.4 (4)	2.3 (1.3–3.9)	Yes	Age, race, education	Hospital-based
La Vecchia *et al.* (1991), Italy	1983–88	562	Highest vs lowest quintile	3.4	Yes	Age, socioeconomic status, smoking, reproductive factors, estrogen use	Hospital-based
Shu *et al.* (1991, 1992), China	1988–90	268	≥ 31.9 vs ≤ 26.2 (4)	2.2 (1.3–3.8)	No	Age, parity	Population-based
Brinton *et al.* (1992) Swanson *et al.* (1993), USA	1987–90	405	≥ 32 vs < 23 (5) > 30 vs < 23 (4)	4.2 (2.5–6.8) 2.0 (1.2–3.3)	Yes No	Age, education, estrogen use, reproductive factors	Population-based
Inoue *et al.* (1994), Japan	1979–92	143	≥24.0 vs < 20 (3)	2.7 (1.6–4.7)	NE	Age	Hospital-based
Olson *et al.* (1995), USA	1986–91	232	≥26.63 vs < 22.61 (3)	3.2 (2.0–5.2)	Yes	Age, reproductive factors, hypertension, diabetes	Population-based
Goodman *et al.* (1997), USA	1985–93	332	≥27.3 vs <21.1 (4)	4.3	Yes	Age, race, reproductive factors, diabetes, total energy	Population-based
Shoff & Newcomb (1998), USA	1991–94	723	≥31.9 vs <29.1 (3)	3.9 (3.1–4.8)	NE	Age, education, diabetes, smoking, estrogen use, parity	Population-based
Parslov *et al.* (2000), Denmark	1987–94	237	≥30 vs < 20 (4)	No association	NE	Age, family history, reproductive factors, estrogen use	Population-based
Weiderpass *et al.* (2000), Sweden	1994–95	709	≥34 + vs <22.5 (6)	6.3 (4.2–9.5)	No	Age, reproductive factors, smoking, estrogen use, diabetes	Population-based

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories
NR, not reported
NE, not estimated

Few studies have examined the association between weight and endometrial cancer separately for pre- and postmenopausal women or by age-group and the numbers of premenopausal women studied have been small. Most of these studies found increased risk in all groups, with somewhat greater risk estimates for older women (La Vecchia *et al.*, 1991; Le Marchand *et al.*, 1991a; Törnberg & Carstensen, 1994). However, in one study (Brinton *et al.*, 1992), the increase in risk was similar for younger and older women and in another study the association with obesity appeared stronger in premenopausal women (La Vecchia *et al.*, 1984). Studies that examined the relationship between body weight at an early age and endometrial cancer found either no association or a weaker association compared with the results for body weight in late adulthood (Henderson *et al.*, 1983; Le Marchand *et al.*, 1991a; Swanson *et al.*, 1993; Olson *et al.*, 1995; Terry *et al.*, 1999; Weiderpass *et al.*, 2000).

Weight gain during adulthood has generally been found to be associated with endometrial cancer risk independently of young adult obesity and in a dose-dependent manner (Le Marchand *et al.*, 1991a; Shu *et al.*, 1992; Swanson *et al.*, 1993; Olson *et al.*, 1995; Terry *et al.*, 1999). In four of the five studies that reported on this variable, the association with adult weight gain remained after adjustment for early-age weight (Le Marchand *et al.*, 1991a; Swanson *et al.*, 1993; Olson *et al.*, 1995; Terry *et al.*, 1999). Since, in most women, adult weight gain represents added fat tissue, it may be a better measure of adiposity than BMI, which reflects the weight of both fat and lean tissue. The linear dose–response relationship with weight gain suggests that any amount of adiposity contributes to endometrial cancer risk.

The distribution of body fat has been examined in relation to endometrial cancer risk using various measures, including WHR, waist-to-thigh ratio, subscapular skinfold and subscapular-to-thigh skinfold ratio. In a cohort study in Iowa, USA, WHR did not contribute additionally to BMI to the risk of endometrial cancer (Folsom *et al.*, 1989). Similarly, in a cohort study conducted in Sweden, WHR did not remain associated with endometrial cancer after adjustment for BMI (Lapidus *et al.*, 1988). Six case–control studies have examined the association of WHR with endometrial cancer. In three of these (Elliott *et al.*, 1990; Schapira *et al.*, 1991; Swanson *et al.*, 1993), WHR was independently associated with risk of the disease, whereas in the three other studies (Austin *et al.*, 1991; Shu *et al.*, 1992; Goodman *et al.*, 1997), this association did not remain statistically significant after adjustment for BMI. However, waist and hip circumferences may not be the most relevant measures of central obesity with regard to endometrial cancer risk. In a hospital-based case–control study in Alabama (Austin *et al.*, 1991) and a population-based case–control study in China (Shu *et al.*, 1992), measures based on subscapular skinfold were found to better predict endometrial cancer risk than WHR, with a threefold increase in risk across quartiles that remained unaffected by adjustment for BMI.

One study has examined the interaction between body weight and estrogen replacement therapy (La Vecchia *et al.*, 1982). Although the power of this study to detect an interaction was small, the effects of estrogen replacement therapy and of body weight on endometrial cancer appeared to be additive.

In conclusion, a direct association between body weight and endometrial cancer has been observed in all but three of 25 epidemiological studies, including in studies conducted in North America, Europe and Asia, and among pre- and postmenopausal women. Overweight women (BMI > 25 kg/m^2 or more) appear to be at a 2–3-fold increased risk of endometrial cancer. Adult weight gain, which may be a better measure of middle-age obesity than BMI, has been found to be associated with risk in a linear dose-dependent fashion. There is evidence that fat distribution may also be important in endometrial cancer, with upper-body obesity particularly increasing risk.

Ovarian cancer

Since the relationship between obesity and ovarian cancer has been examined in only a relatively small number of cohort and case–control studies (Table 30), all but the smallest studies (less than 50 cases) were considered in this review. A potential methodological problem that may be particularly significant for ovarian cancer is the possibility of reverse causation, i.e., that a weight loss due to preclinical disease may confound an association with body weight.

Cohort studies

Lew and Garfinkel (1979) reported a statistically significant 1.63-fold increased risk of mortality from ovarian cancer in women with weight >40% above average compared with women of average weight in the American Cancer Society cohort study. However, Møller *et al.* (1994) found no increased risk of ovarian cancer in a cohort of obese women, compared with the Danish population. Similarly, a large cohort study of Swedish women (Törnberg & Carstensen, 1994) with 330 cases found no association with BMI (RR = 1.0; 95% CI 0.92–1.1). A report based on 97 cases and seven years of follow-up from the Iowa Women's Health Study (Mink *et al.*, 1996), which included information on possible confounders, also showed no association of BMI with ovarian cancer (RR = 1.1; 95% CI 0.64–1.9).

Case–control studies

The results of case–control studies have also been inconsistent (Table 30), with five studies finding a direct association (Casagrande *et al.*, 1979; CASH Study,

Table 30. Studies of body mass index and risk of ovarian cancer

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend*	Adjustment for confounding	Comments
Cohort studies							
Lew & Garfinkel (1979), USA	1959–72		40% > average weight	1.6	NE	Age	Mortality study
Møller *et al.* (1994), Denmark	1977–87	58	Incidence relative to population	1.1 (0.8–1.4)	NE	Age, calendar period	Cohort of obese women
Törnberg & Cartensen (1994), Sweden	1963–87	330	≥ 28 vs < 22 (5)	1.0 (0.92–1.1)	No	Age, period of follow-up	Cancer registry
Mink *et al.* (1996), USA	1985–92	97	>29.51 vs <23.45 (4)	1.1 (0.64–1.9)	No	Age	Age 55–69 yrs
Case–control studies							
Casagrande *et al.* (1979), USA	1973–76	150	20% > ideal weight	2.1	NE	Age, 'ovulatory age'	Population-based
Byers *et al.* (1983), USA	1957–65	274	> 30 vs < 21.5 (5)	0.74	No	Age	Hospital-based
CASH Study (1987), USA	1980–82	546	> 25.0 vs < 22.5 (3)	Direct association	NE	Age	Population-based
Mori *et al.* (1988), Japan	1980–86	110	> 20 vs ≤ 20	1.7 (0.9–3.3)	NE	Age	Hospital-based
Farrow *et al.* (1989), USA	1976–79	277	≥ 24.1 vs <19.8 (5)	1.7 (1.1–2.7)	Yes	Age, parity, estrogen use	Population-based
Hartge *et al.* (1989), USA	1978–81	296	Highest vs lowest quartile	1.1	No	Age, race	Hospital-based
Shu *et al.* (1989),	1984–86	172	≥ 22.32 vs ≤ 18.86 (4)	1.6 (0.8–3.3)	No	Age, education, animal fat intake	Population-China based
Purdie *et al.* (1995), Australia	1990–93	824	≥ 85th vs < 15th percentile	2.0 (1.4–2.8)	Yes	Age, reproductive factors, estrogen use	Population-based
Parazzini *et al.* (1997), Italy	1983–91	971	Severe overweight or obesity: yes vs no	0.66 (0.52–0.85)	NE	Age, education, reproductive factors	Hospital-based
Mori *et al.* (1998), Japan	1994–96	89	≥ 25.9 vs ≤ 21.9 (4)	1.6 (0.80–3.0)	No	Age, marital status	Hospital-based

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories

1987; Farrow *et al.*, 1989; Purdie *et al.*, 1995; Mori *et al.*, 1998), four showing no association (Byers *et al.*, 1983; Mori *et al.*, 1988; Hartge *et al.*, 1989; Shu *et al.*, 1989) and one showing an inverse association (Parazzini *et al.*, 1997). The two largest case–control studies found clearly divergent results. The study by Purdie *et al.* (1995) conducted in Australia found a twofold increased risk of ovarian cancer (95% CI 1.4–2.8) for women with BMI above the 85th percentile whereas, in their study in Italy, Parazzini *et al.* (1997) reported a decreased risk (OR = 0.66; 95% CI 0.52–0.85) for women with "severe overweight".

Discussion

The evidence from the relatively few studies on body weight and ovarian cancer has been inconsistent and does not allow any conclusion to be drawn on a possible association.

In addition to BMI, measures of central obesity were examined in two cohort studies in relation to ovarian cancer risk. Lapidus *et al.* (1988) found no association between this cancer and WHR or subscapular skinfold in a small cohort of Swedish women after adjusting for BMI. In contrast, Mink *et al.* (1996) found a 2.3-fold increased risk of ovarian cancer (95% CI 1.2–4.5) for women in the fourth quartile of WHR compared with the lowest quartile in a cohort study in Iowa, USA. In this study, no association was found with BMI and the association with WHR was not attenuated by adjustment for other risk factors.

Prostate cancer

Although prostate cancer is a common cancer in many developed countries, very few risk factors have been identified for this disease. Because rates of the disease increase when migrants move from low-risk to high-risk areas, lifestyle and diet are thought to play major roles in its etiology. Much attention has been given to the possible importance of nutrition, and in particular obesity and physical activity. Because latent or early-stage prostate tumours are often found at autopsy, the clinical significance of early-stage prostate cancer, as commonly detected by screening, is unclear. Also, it is possible that lifestyle characteristics that are associated with participation in screening may confound studies of other risk factors. Thus, analyses that focused on the more aggressive, high-grade tumours are particularly useful.

Cohort studies

Table 31 summarizes the prospective studies with at least 100 cases which have explored the relationship between anthropometric variables and prostate cancer. Most of these studies focused on adult weight and BMI. Four cohort studies found a direct association between weight or BMI and prostate cancer (Lew & Garfinkel, 1979; Chyou *et al.*, 1994; Andersson *et al.*, 1997; Putnam *et al.*, 2000). However, nine other cohort studies found no statistically significant association between body mass and prostate cancer (Greenwald *et al.*, 1974; Whittemore *et al.*, 1985a; Mills *et al.*, 1989; Thompson *et al.*, 1989; Le Marchand *et al.*, 1994; Giovannucci *et al.*, 1997; Lund Nilsen & Vatten, 1999; Schuurman *et al.*, 2000; Clarke & Whittemore, 2000). Although the majority of the significant associations with body mass were found in studies which focused on fatal or more aggressive tumours (Greenwald *et al.*, 1974; Andersson *et al.*, 1997; Putnam *et al.*, 2000), a clear pattern of a stronger association for the more clinically significant forms of the disease has not been consistently observed. Some studies having death from prostate cancer as the endpoint did not find any association with BMI (Greenwald *et al.*, 1974; Whittemore *et al.*, 1985) and some large cohorts which conducted sub-group analyses on advanced prostate cancer did not clearly show a stronger effect for BMI in these patients (Giovannucci *et al.*, 1997; Lund Nilsen & Vatten, 1999).

Three large, well conducted prospective studies illustrate the variation in the epidemiological findings on body weight and prostate cancer. In a retrospective cohort study, Andersson *et al.* (1997) studied 135 000 Swedish construction workers who participated in health check-ups between 1971 and 1975 and were followed through 1991. A total of 2368 incident prostate cancer cases and 708 deaths from this disease were observed. Height and weight were measured at baseline. Weak positive associations (13–17% increase in risk for the highest compared with the lowest quartile) were found for weight, height, BMI and estimated lean body mass. These associations were somewhat stronger (30–40% increase in risk) when prostate cancer death rather than incidence was used as the endpoint. Giovannucci *et al.* (1997) analysed data from the Health Professionals Follow-up Study, a cohort of 47 781 men who answered a mail questionnaire in 1986 and were followed until 1994. They identified 1369 cases of incident prostate cancer. Adult body mass was unrelated to the risk of total, advanced or metastatic prostate cancer. In contrast, higher BMI at age 21 years was associated with a significantly lower risk of advanced (RR = 0.53; 95% CI 0.33–0.86 for BMI ≥26 vs <20 kg/m^2 at age 21 years) and metastatic prostate cancer. Schuurman *et al.* (2000) used data from the Netherlands Cohort Study to investigate by a case–cohort approach the relationship of anthropometric variables with prostatic cancer. They studied 58 279 men aged 55–69 years who completed a self-administered questionnaire in 1986 and were followed until 1992. A total of 681 incident cases were identified. No association was found with baseline BMI, height or lean body mass for total, localized or advanced prostate cancer. However, a direct association was observed between BMI at age 20 years

Table 31. Studies of body mass index and risk of prostate cancer

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend	Adjustment for confounding	Comments
Cohort studies							
Greenwald *et al.* (1974), USA	1880–1916	268	Mean BMI	No association	NE	Age	Mortality study
Lew & Garfinkel (1979), USA	1959–72	NR	40% > average weight	1.3	No	Age	Mortality study
Whittemore *et al.* (1985), (1985), USA	1916–78	243	NR	No association	NE	Age	Mortality study
Mills *et al.* (1989), USA	1976–82	180	>25.9 vs ≤23.2 (3)	1.2 (0.79–1.7)	No	Age	7th day Adventists
Thompson *et al.* (1989a), USA	1972–87	100	BMI per 2.92 kg/m^2	1.2 (1.0–1.5)	NE	Age, diabetes, family history, systolic blood pressure, diet, smoking	Age 50–84 yrs
Chyou *et al.* (1994), USA	1965–92	306	Weight ≥ 70 + vs <57 kg (4)	1.5 (1.1–2.1)	Yes	Age	Hawaii Japanese
Le Marchand *et al.* (1994), USA	1975–89	198	> 26 vs < 22 (4)	0.7 (0.5–1.2)	No	Age, ethnicity, income	Hawaii residents
Giovannucci *et al.* (1997), USA	1986–94	1369	≥29 vs <23 (7)	0.90 (0.71–1.2)	No	Age, height	Health professionals
Andersson *et al.* (1997), Sweden	1971–91	2368	>26.2 vs <22.1 (4)	1.1 (0.99–1.3)	No	Age	Construction workers
Lund Nilsen & Vatten (1999), Norway	1984–97	642	≥28.3 vs ≤23.0 (5)	1.0 (0.8–1.3)	No	Age	Health screenees
Clarke & Whittemore (2000), USA	1971–92	201	Mean BMI	No association	No	Age, race	Caucasians (2000), African Americans
Putnam *et al.* (2000), USA	1986–95	101	> 26.6 vs <24.1 (3)	1.6 (0.9–2.8)	No	Age, diet, family history	Cancer registry
Schuurman *et al.*(2000), Netherlands	1986–92	681	≥28 vs <22 (5)	0.89 (0.58–1.4)	No	Age, family history, socioeconomic status	Age 55–69 yrs
Case–control studies							
Wynder *et al.* (1971), USA	1968–69	300	Relative weight	No association	NE	Age	Hospital-based

Table 31 (contd)

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend	Adjustment for confounding	Comments
Graham *et al.*(1983), (1983), USA	1957–65	311	BMI distribution	No association	NE	Age	Hospital-based
Talamini *et al.* (1986), Italy	1980–83	166	≥ 28 vs < 23 (3)	4.4 (1.9–9.9)	Yes	Age, marital status, occupation, diet	Hospital-based
Ross *et al.* (1987), USA	1977–80	142	Mean BMI	No association	NE	Age, ethnicity	Population-based
Kolonel *et al.* (1988), USA	1977–83	452	Mean BMI	No association	NE	Age, ethnicity	Population-based; Hawaii
West *et al.* (1991), USA	1984–85	358	Highest vs lowest quartile	No association	NE	Age	Population-based
Andersson *et al.* (1995, 1996), Sweden	1989–92	256	> 23.81 vs ≤20.83 (4) > 27.36 vs ≤ 23.84 (4)	1.0 (0.6–1.8) 1.2 (0.7–2.0)	No No	Age, region	Population-based
Whittemore *et al.* (1995), USA, Canada	1987–91	1655	Mean BMI	No association	NE	Age, race, ethnicity	Population-based
Grönberg *et al.* (1996), Sweden	1967–70	406	> 29 vs ≤23 (4)	1.8 (1.1–3.0)	Yes	Age, diet	Twin registry
Ilic *et al.* (1996), Yugoslavia	1990–94	101	≥ 28 vs < 22 (3)	No association	No	Age	Hospital-based
Key *et al.* (1997), United Kingdom	1989–92	328	Age 45 y, > 25.17 vs <22.75 (3)	1.4 (0.95–2.0)	No	Age	Population-based
Hsieh *et al.* (1999), Greece	1994–97	320	≥ 32 vs < 20 (8)	No association	No	Age, education	Hospital-based
Sung *et al.* (1999), Taiwan	1995–96	90	Age 40–45 y, >24.75 vs ≤24.75	0.50 (0.26–0.95)	NE	Age, education, exercise, diet	Hospital-based
Villeneuve *et al.* (1999), Canada	1994–97	1623	≥ 30 vs < 20 (4)	0.9 (0.7–1.1)	No	Age, ethnicity, residence, smoking, diet, income	Population-based
Hsing *et al.* (2000), China	1993–95	238	≥24.03 vs <19.82 (4)	1.2 (0.73–1.8)	No	Age, education, marital status, total energy intake	Population-based

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories
NR, not reported
NE, not estimated

and prostate cancer (RR = 1.3; 95% CI 0.81–2.2 for BMI ≥25 vs. <19 kg/m^2 at age 20 years). This association was limited to localized tumours and not observed for advanced tumours.

Case–control studies

Case–control studies of body mass and prostate cancer risk (Table 31) have been quite consistent in suggesting no association (Wynder *et al.*, 1971; Graham *et al.*, 1983; Ross *et al.*, 1987; Kolonel *et al.*, 1988; West *et al.*, 1991; Whittemore *et al.*, 1995; Andersson *et al.*, 1995, 1996; Ilic *et al.*, 1996; Key *et al.*, 1997; Hsieh *et al.*, 1999; Villeneuve *et al.*, 1999; Hsing *et al.*, 2000). Some of these studies were particularly large and informative. A population-based case–control study conducted by Whittemore *et al.* (1995) among 1655 cases and 1645 controls of African American, Asian or Caucasian origin, in California, Hawaii and Canada showed a clear lack of association with BMI. Similarly, the population-based case–control study conducted by Villeneuve *et al.* (1999) in eight Canadian provinces with 1623 cases and 1623 controls found an odds ratio of 0.9 (95% CI 0.7–1.1) for men with BMI >30 kg/m^2, compared with those having BMI <20 kg/m^2. Another population-based case–control study conducted in China reported an odds ratio of 1.2 (95% CI 0.73–1.8) for BMI >24.03 kg/m^2 compared with BMI ≤19.82 kg/m^2 (Hsing *et al.*, 2000).

Not all studies have been null, however. Two case–control studies conducted in Italy (Talamini *et al.*, 1986) and Sweden (Grönberg *et al.*, 1996) reported a direct association, and one in Taiwan (Sung *et al.*, 1999) reported an inverse association between BMI and prostate cancer.

Discussion

It is possible that adult weight and BMI do not well reflect the actual exposures most relevant to prostate cancer etiology. BMI reflects both lean body mass and adipose tissue, especially in men, and thus is not an ideal measure for studies of an androgen-dependent tumour, such as prostate cancer, since lean body mass is related to androgen levels. Only a few studies have investigated the body fat distribution patterns that may be more strongly related to the endocrine abnormalities typically associated with obesity. Giovannucci *et al.* (1997) failed to find an association between waist circumference or WHR and prostate cancer. However, they found a borderline statistically significant inverse association with hip circumference. No association with waist girth was found in a large case–control study conducted in California, Hawaii and Canada (Whittemore *et al.*, 1995). In contrast, a population-based cohort study conducted in China reported a direct dose-dependent association with WHR, with an OR of 2.7 (95% CI 1.7–4.4) for a WHR >0.92, compared with ≤0.86 (Hsing *et al.*, 2000).

It is also possible that body mass at a young age is more important than adult BMI. However, the results on body weight in young adulthood have also been inconsistent, with a large cohort study finding a weak direct association between BMI at age 20 years and prostate cancer (Schuurman *et al.*, 2000), one cohort study (Cerhan *et al.*, 1997) and two case–control studies (Andersson *et al.*, 1996; Key *et al.*, 1997) finding no association and another large cohort study finding an inverse association with advanced disease (Giovannucci *et al.*, 1997). A reduced risk was also associated in the latter study with obesity at ages 5 and 10 years, based on self-reported assessment using pictograms of body size and shape. Height, which partially reflects energy intake in childhood and androgen levels around the time of puberty, has been more intensively investigated. Four cohort studies (Le Marchand *et al.*, 1994; Andersson *et al.*, 1997; Giovannucci *et al.*, 1997; Hebert *et al.*, 1997) found a direct association between attained adult height and prostate cancer. However, six other cohort studies (Whittemore *et al.*, 1985; Severson *et al.*, 1988; Cerhan *et al.*, 1997; Veierod *et al.*, 1997; Lund Nilsen & Vatten, 1999; Clarke & Whittemore, 2000) and all but one case–control studies (Norrish *et al.*, 2000) that have reported on height failed to find an association.

High birth weight was found to be associated with increased risk of prostate cancer in a small cohort study in Sweden that used midwife records (Tibblin *et al.*, 1995). An attempt to reproduce this finding using self-reported birth weight in a large cohort study in the USA found no overall association with prostate cancer, although a weak association between birth weight and high-stage/grade tumours was suggested (Platz *et al.*, 1998). Thus, measures of body mass during childhood, adolescence or early adulthood have not been consistently associated with prostate cancer risk, mirroring the inconclusive results obtained for adult body mass.

In summary, a quite large number of studies have examined the association between body weight and prostate cancer in a variety of populations in North America, Europe and Asia, and have considered weight at different periods of life as well as body fat distribution. Some studies focused on the more aggressive forms of the disease which may be less subject to detection bias. No consistent pattern of association has emerged. The data suggest the absence of an important association between elevated body weight and the risk of prostate cancer.

Kidney cancer

Several studies worldwide have established BMI as a risk factor for renal-cell cancer (Bergström *et al.*, 2001) (Table 32) Additionally, diabetes and hypertension, which are both related to obesity, are established risk factors for renal-cell cancer. In contrast, no association between obesity and tumours of the renal

pelvis has been identified (McCredie & Stewart, 1992; Chow *et al.*, 2000).

Cohort studies

Four studies based on at least 100 kidney cancer cases (Finkle *et al.*, 1993; Hiatt *et al.*, 1994; Heath *et al.*, 1997; Chow *et al.*, 2000) conducted in North America and Sweden have reported on the association between obesity and kidney cancer. Among women in the Kaiser Foundation Health Plan between 1980 to 1989, Finkle *et al.* (1993) identified 191 cases of histologically verified renal-cell cancer. The earliest recorded measure of weight/height was compared. Renal-cell cancer was associated with increasing relative weight, with a 2.6-fold increased risk in the highest quartile compared with the lowest and a significant trend ($p < 0.01$). In a similar study, Hiatt *et al.* (1994) identified 167 male and 90 female cases of renal-cell cancer that occurred between 1964 and 1988 among participants of the Kaiser Permanente Medical Care Program in northern California. Among neither men nor women was any increase in renal-cell cancer with BMI observed. Following 998 904 men and women for seven years (1982–89), Heath *et al.* (1997) identified 212 and 123 renal-cell cancer deaths among men and women, respectively. High BMI was associated with increased mortality from renal-cell cancer, in both men and women. In a study based on the health records of 363 992 Swedish male construction workers who underwent at least one physical examination between 1971 and 1992, Chow *et al.* (2000) identified 759 renal-cell cancer cases, as well as 136 cases of renal pelvis cancer. The risk of renal-cell cancer was significantly higher in those with a high BMI, with an approximate doubling of risk among those in the highest octile of the cohort compared with the lowest. A dose–response relationship was observed. No association was observed between BMI and cancer of the renal pelvis.

Case–control studies

Fifteen case–control studies covering populations in North America, northern and southern Europe, Asia and Australia have reported on the association between BMI and renal-cell cancer (Table 32). Four of these (McLaughlin *et al.*, 1984; McCredie & Stewart, 1992; Lindblad *et al.*, 1994; Mellemgaard *et al.*, 1994) were included in a pooled analysis of 1050 male and 682 female renal-cell cancer cases, which provides the most accurate estimates of the relationship between BMI and renal-cell cancer (Mellemgaard *et al.*, 1995). In this pooled analysis, including studies conducted in Australia, Denmark, Germany, Sweden and the USA, an increasing trend in renal-cell cancer with increasing BMI was observed for both men and women, with a 3.6-fold increased risk for women and a 1.6-fold increased risk for men in the fourth quartile of BMI compared with the first. In the remaining 11 case–control studies, an increasing risk of renal-cell cancer with BMI was observed either in men or women or in both in nine studies, an exception being a small hospital-based case–control study in northern Italy (Talamini *et al.*, 1990). As well as the international pooled study which reported a greater effect of BMI among women than among men, four of the remaining studies provided evidence of a stronger association among women (McLaughlin *et al.*, 1992; Benhamou *et al.*, 1993; Kreiger *et al.*, 1993; Chow *et al.*, 1996), while one showed a greater effect among men (Asal *et al.*, 1988).

Discussion

A consistently increased risk of renal-cell cancer with increasing BMI, with a dose–response relationship, was observed in most studies for both men and women. Furthermore, it was observed both in a large case–control study (Yuan *et al.*, 1998) and in a cohort study (Chow *et al.*, 2000) that obesity, independently of blood pressure, increased renal-cell cancer risk. This may indicate that obesity and hypertension influence renal-cell cancer through different mechanisms.

BMI has been observed in some studies to increase renal-cell cancer risk more among women than men (McLaughlin *et al.*, 1992; Mellemgaard *et al.*, 1994). This suggests the importance of gender-specific fat distribution and hormonal levels. A high WHR has been observed in two studies to increase renal-cell cancer risk (Prineas *et al.*, 1997; Bergström, 2001).

Weight change throughout life has been investigated in a population-based case–control study; subjects with a high BMI already at age 20 years who further gained 20 kg or more between ages 20 and 50 years had a 2.9-fold increased risk (95% CI 1.4–6.0) (Bergström, 2001). Those with a low BMI at age 20 years who gained weight up to age 50 years had a moderately increased risk of renal-cell cancer. Both weight cycling and weight loss have been observed to increase renal-cell cancer risk (Mellemgaard *et al.*, 1995; Bergström, 2001). Losing weight was associated with increase in risk, especially among subjects with low BMI at age 20 years (RR = 2.6, 95% CI 1.4–4.7) (Bergström, 2001). These observations of increased risk of renal-cell cancer with weight loss may be explained by incomplete adjustment for preclinical disease.

In a recent meta-analysis including 11 studies, 6% and 7% increases in renal-cell cancer risk were observed for each unit increase in BMI in men and women, respectively. The estimated relative risks correspond to increases in risk of 36% for an overweight person (BMI >25.0 kg/m^2) and 84% for an obese person (BMI >30.0 kg/m^2 (Bergström *et al.*, 2001).

In summary, all studies except for one of the 19 reviewed found a more than twofold increase in renal-cell cancer risk among obese men and women compared with those of normal weight. The studies, conducted in Australia, China, Europe and the USA, consistently found

Table 32. Studies of body mass index and risk of renal-cell cancer

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend	Adjustment for confounding	Comments
Cohort studies							
Finkle *et al.* (1993), USA	1980–89	F: 161	Weight/height F: ≥75 vs <25 (4)	2.6 (1.4–4.8)	Yes	Age	Medical care programme
Hiatt *et al.* (1994), USA	1964–88	M: 163 F: 88	M: ≥28.3 vs <24.6 (4) F: ≥27.8 vs <21.8 (4)	M: 0.9 (0.5–1.6) F: 1.2 (0.5–2.9)	M: No F: No	Age	Medical care programme
Heath *et al.* (1997), USA	1982–89	M: 208 F: 121	M: ≥31.1 vs ≤24.6 (4) F: ≥32.3 vs ≤21.9 (4)	M: 1.6 (0.9–2.7) F: 3.1 (1.5–6.4)	M: No F: Yes	Age	Mortality study
Chow *et al.* (2000), Sweden	1971–92	M: 759	≥27.8 vs ≤20.8 (8)	1.9 (1.3–2.7)	Yes	Age, smoking status, diastolic blood pressure	No association observed between BMI and renal pelvis cancer (*N*=136)
Case–control studies							
McLaughlin *et al.* (1984), USA	1974–79	M: 310 F: 178	M: >5.72 vs <4.83 lb/ft^2 F: >5.36 vs <4.42 lb/ft^2 (4)	M: 1.3 (0.8–1.8) F: 2.3 (1.3–4.1)	M: No F: Yes	Age, cigarette smoking	Population-based
Goodman *et al.* (1986), USA	1977–83	M: 173 F: 71	≥ 28 vs < 24 (3)	M: 2.7 (1.5–5.9) F: 2.4 (1.2–6.8)	M: Yes F: Yes	Age, saccharin additives, diet beverages, lifetime grams of artificial sweeteners, recreational and occupational activity, history of diabetes	Hospital-based
Asal *et al.* (1988), USA	1981–84	M: 209 F: 100	M: >6.02 vs <4.86 lb/ft^2 F: >6.16 vs <4.60 lb/ft^2 (4)	M: 3.3 (1.8–6.1) F: 1.2 (0.6–2.6)	M: Yes F: No	Age, education	Adjustment for smoking made little difference. Population-based
Maclure & Willett (1990), USA	1976–83	M: 135 F: 68	> 28 vs ≤22 (5)	M: 1.7 (1.1–2.8) F: 1.7 (0.9–3.2)	M: NE F: NE	Income, occupational status, education, history of cardiovascular disease	Population-based
Talamini *et al.* (1990), Italy	1986–89	M: 150 F: 90	>27 vs <24 (3)	0.74 (0.51–1.1)	No	Age, education, area of residence	Hospital-based

Table 32 (contd)

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend	Adjustment for confounding	Comments
McCredie & Stewart (1992), Australia	1989–90	M: 307 F: 173	M: >25.34 vs < 23.05 (3) F: >30.79 vs <27.21 (3)	M: 1.6 (1.1–2.5) F: 1.3 (0.8–2.1)	M: Yes F: No	Age, method of interview	Population-based
McLaughlin *et al.* (1992), China	1987–89	M: 76 F: 58	At age 50 y M: >23.3 vs ≤19.7 (4) F: >30.6 vs ≤24.4 (4)	M: 1.7 (0.5–5.7) F: 3.3 (0.7–15.1)	M: Yes F: No	Age, education, smoking Age, education	Population-based
Benhamou *et al.* (1993), France	1987–91	M: 138 F: 58	≥27 vs ≤20 (4)	M: 2.4 (1.0–5.9) F: 3.5 (1.0–11.8)	M: Yes F: Yes	Age, years at school, smoking	Hospital-based
Kreiger *et al.* (1993), Canada	1986–87	M: 282 F: 181	M: >25.1 vs ≤21.5 (4) F: >23.0 vs ≤19.7 (4)	M: 1.3 (0.8–2.2) F: 2.5 (1.4–4.6)	M: No F: Yes	Age, smoking status, BMI at age 25 y	Population-based
Lindblad *et al.* (1994), Sweden	1989–91	M: 207 F: 172	M: >25.8 vs <23.1 (4) F: >25.2 vs <21.3 (4)	M: 1.4 (0.78–2.4) F: 1.4 (0.71–2.9)	M: No F: No	Age, education, smoking, amphetamine use, weight cycling	Population-based
Mellemgaard *et al.* (1994), Denmark	1989–91	M: 225 F: 141	M: >26.4 vs <23.1 (4) F: >31.7 vs <27.2 (4)	M: 1.2 (0.7–2.0) F: 2.2 (1.1–4.2)	M: No F: No	Age, smoking, socio-economic status	Population-based
Muscat *et al.* (1995), USA	1977–93	M: 543 F: 245	Highest vs lowest quartile	M: 1.4 (1.1–1.9) F: 1.4 (0.9–2.1)	NE NE	Age, education, smoking	Hospital-based
Chow *et al.* (1996), USA	1988–90	M: 274 F: 163	Highest vs lowest quintile	M: 1.3 (0.7–2.3) F: 3.8 (1.7–8.4)	M: No F: Yes	Age, smoking, history of hypertension/hypertensive drug use	Population-based
Boeing *et al.* (1997), Germany	1989–91	259	>27 vs <25 (3)	2.2 (1.3–3.8)	Yes	Age, gender, smoking, alcohol, education	Population-based
Yuan *et al.* (1998), USA	1986–94	M: 781 F: 423	≥ 30 vs <22 (6)	M: 4.6 (2.9–7.5) F: 4.0 (2.3–7.0)	M: Yes F: Yes	Age, education	Population-based

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories
NE, not estimated; 1 lb/ft^2 = 4.9 kg/m^2

the risk of renal-cell cancer to increase in a BMI-dependent manner in both men and women.

Lung cancer

A positive association between overweight and cancer mortality has been well documented for both men and women (Lew & Garfinkel, 1979; Waaler, 1984; Møller *et al.*, 1994; Calle *et al.*, 1999) (Table 33). In contrast, there has been considerable debate as to whether lower body weight is associated with either higher total mortality (Lee *et al.*, 1993) or lung cancer risk (Waaler, 1984; Goodman & Wilkens, 1993). Inclusion of individuals with pre-existing respiratory diseases and/or smoking-related weight loss may explain a U-shaped or a J-shaped relationship between body weight and cancer mortality rates observed in many studies (Singh & Lindsted 1998). Thus, the issue of whether body weight is related to increased risk of lung cancer remains controversial.

Cohort studies

Five cohort studies that investigated the association between weight and lung cancer risk were conducted in Finland (Knekt *et al.*, 1991), the USA (Lee & Paffenbarger, 1992b; Chyou *et al.*, 1994; Drinkard *et al.*, 1995) and Israel (Kark *et al.*, 1995). During 19 years of follow-up, 504 lung cancer cases were diagnosed among 25 994 Finnish men (Knekt *et al.*, 1991). An inverse association between BMI and lung cancer risk was observed overall after adjustment for potential confounding factors including smoking and was even stronger among non-smokers. Lee and Paffenbarger (1992b), in a study of Harvard alumni including 286 lung cancer cases diagnosed between 1962/66 and 1988, observed a nearly twofold increase in lung cancer risk among those in the lowest tertile compared with the highest tertile of BMI, with a dose–response association in the first 11–15 years of follow-up. In a linkage study including 9975 male civil servants, BMI was inversely related to lung cancer incidence in a dose-dependent manner, with a relative risk of 0.44 (95% CI 0.26–0.72) for the highest quintile of BMI compared with the lowest (Kark *et al.*, 1995). Controlling for lung function did not change the association observed. In the study by Chyou *et al.* (1994), including 236 lung cancer cases, a clear inverse association between skinfold thickness and lung cancer risk was observed, but no association between BMI and lung cancer risk was seen after adjustment for smoking habits. In a prospective study of women in Iowa, USA (Drinkard *et al.*, 1995), BMI was estimated through self-reporting at ages 18, 30, 40 and 50 years and at baseline. Among never-smokers, no association between BMI at baseline and lung cancer risk was observed among 233 lung cancer cases diagnosed during six years of follow-up.

Case–control studies

In a hospital-based case–control study including 3607 lung cancer cases, no significant association was observed in men who never smoked between the highest and lowest quartiles of BMI and lung cancer risk (RR = 1.1, 95% CI 0.5–2.5) (Kabat & Wynder, 1992). In contrast, in currently smoking men, after adjustment for smoking habits, a twofold decreased risk was observed (RR = 0.5; 0.4–0.7). However, a clear inverse dose–response relationship was observed between BMI and lung cancer risk in both currently smoking and never-smoking women. A population-based case–control study in Hawaii found an inverse association with BMI assessed only five years before diagnosis but not with BMI at ages 20 or 29 years, with an increased risk among the leanest men and women (Goodman & Wilkens, 1993). Information about preclinical disease was not available. A population-based case–control study in the USA included subjects who either had not smoked more than 100 cigarettes during their lifetime (never smokers) or had not smoked during the past 10 years (former smokers) (Rauscher *et al.*, 2000). Those in the highest octile of BMI (> 30.8 kg/m^2) had more than twice the odds of developing lung cancer compared with those in the lowest octile (BMI ≤ 21.3 kg/m^2).

Discussion

An inverse dose–response relationship between BMI and lung cancer was observed overall or in most subgroups in all studies except one (Rauscher *et al.*, 2000) of those reviewed. However, several cohort studies suggested that an inverse association between BMI and lung cancer risk is limited to those who developed lung cancer in the first years of follow-up (Lee & Paffenbarger, 1992b; Drinkard *et al.*, 1995). Thus, the inverse association observed between BMI and lung cancer may be explained by weight loss due to preclinical disease, i.e., latent undiagnosed lung cancer. This is supported by the observation that the inverse association between skinfold thickness and lung cancer did not persist as the time between examination and cancer diagnosis was lengthened (Chyou *et al.*, 1994).

Since smoking is well established as the primary cause of lung cancer and is inversely associated with BMI, the inverse association between BMI and lung cancer may reflect incomplete adjustment for effects of smoking. This is supported by the observation that no significant association between BMI and lung cancer risk was observed among men who never smoked, while among currently smoking men, after adjustment for smoking habits, an increased lung cancer risk was observed with higher BMI. In the cohort study by Drinkard *et al.* (1995), multivariate analyses suggested that the inverse association of BMI with lung cancer could be explained by smoking status and that the positive association between WHR and lung cancer with lung cancer could be explained in terms of pack-years of smoking.

Table 33. Studies of body mass index and risk of lung cancer

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend*	Adjustment for confounding	Comments
Cohort studies							
Knekt *et al.* (1991), Finland	1966–84	M: 504	> 27.0 vs ≤ 22.5 (4)	0.55 (0.42–0.71)	Yes	Age, geographical area, social class, smoking, general health, number of stress symptoms, chest X-ray	Screening examination
Lee & Paffenbarger (1992b), USA	1962–88	M: 286	≥ 25.0 vs <22.0 (3)	Current smokers: 1962/66–77: 0.54 (0.30–0.99) 1978–88: 0.97 (0.57–1.7)	 Yes No	Age, smoking, number of cigarettes per day, physical activity	Age 40–69 years
Chyou *et al.* (1994), USA	1965–92	M: 236	≥ 26.0 vs <22.0 (4)	0.69 (0.46–1.0)	No	Age, smoking	Hawaii Japanese
Drinkard *et al.* (1995), USA	1986–92	F: 233	Total population >29.7 vs <23.5 (4) Never smokers >28.4 vs <24.3 (4)	0.52 (0.36–0.74) 0.68 (0.31–1.5)	Yes No	Age, education, physical activity, alcohol, pack-years, years since last smoked	Effect not seen for non-smokers Age 55–69 years
Kark *et al.* (1995), Israel	1963–86	M: 153	≥22.9 vs < 20.2 (5)	0.44 (0.26–0.72)	Yes	Age, smoking, city of employment	Smokers included
Case–control studies							
Kabat & Wynder (1992), USA	1981–90	M: 69 F: 127	≥28 vs < 22 (4)	Never-smokers M: 1.1 (0.5–2.5) F: 0.34 (0.2–0.6)	 M: No F: Yes	Age, education, race, hospital, history of chronic lung disease, alcohol	Hospital-based
Goodman & Wilkens (1993), USA	1979–85	M: 518 F: 230	M: >25.8 vs <21.9 (4) F: >25.5 vs <20.2 (4)	0.6 (0.4–0.8) 0.6 (0.4–1.0)	Yes Yes	Age, ethnicity, smoking	Population-based
Rauscher *et al.* (2000), USA	1982–85	M+F: 188	>30.8 vs ≤21.3 (8)	M: 2.6 (0.8–7.9) F: 2.1 (0.9–4.8)	NE	Age, years of smoking, number smoked per day, education	Population-based

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories

Oesophageal cancer

During recent decades, the incidence of oesophageal and gastric cardia adenocarcinoma has been increasing, while the incidence of oesophageal squamous cell carcinoma has remained relatively constant. Except for an association with Barrett's oesophagus, little is known about the etiology of these cancers. Certain epidemiological and molecular differences between oesophageal and gastric cardia carcinoma suggest that these cancers represent biologically different malignancies (Dolan *et al.*, 1999; Wijnhoven *et al.*, 1999).

Cohort studies

Data from the national Norwegian screening programme for tuberculosis (Tretli & Robsahm, 1999) were used in a study of 1 100 000 individuals aged 30–69 years at the time of examination who were followed until December 1989 (Table 34). High BMI was associated with increased risk of oesophageal adenocarcinoma, while the incidence of squamous cell carcinoma was linked to low BMI (men, RR = 2.4; 95% CI 1.3–4.4; women, RR = 1.6; 95% CI 0.5–4.8 for the highest quintiles).

Case–control studies

Out of eight reported case–control studies, six included more than 100 cases (Table 34). In a study of 173 male cases with adenocarcinoma of the distal oesophagus or cardia and 4544 controls, Kabat *et al.* (1993) found no association with reported BMI five years before diagnosis (BMI ≥28 vs <22 kg/m^2: OR = 0.8; 95% CI 0.4–1.7) for adenocarcinoma of the oesophagus or cardia. A smaller study by Zhang *et al.* (1996) also failed to find an association between BMI and oesophageal cancer. However, five case–control studies have observed positive associations with increasing BMI. In the US study of Brown *et al.* (1995), 162 male cases with oesophageal adenocarcinoma were compared with 685 controls. Risk was significantly elevated for subjects in the heaviest quartile compared to the lowest quartile of BMI, (OR = 3.1; 95% CI 1.8–5.3). Vaughan *et al.* (1995) studied 133 cases of adenocarcinoma of the oesophagus and 165 cases of cancer of the gastric cardia and found increased risks with higher BMI (OR = 2.5; 95% CI 1.2–5.0 and 1.6; 95% CI 0.8–3.0, respectively for the highest percentiles of BMI). Ji *et al.* (1997) reported ORs for adenocarcinoma of the cardia of 5.4 (95% CI 2.4–12.3) for men and 1.8 (95% CI 0.5–6.4) for BMI above 25 kg/m^2 in women in Shanghai, China. Chow *et al.* (1998) also found increasing risk associated with BMI for both oesophageal adenocarcinoma and gastric cardia adenocarcinoma. The elevated risk was related mainly to excess weight *per se* and not to weight change over time. Men in the highest quartile of usual BMI had an OR of 3.0 (95% CI 1.7–5.0) and women OR 2.6 (95% CI 0.8–8.5) for oesophageal adenocarcinoma, while the ORs for cardia cancer were lower. The ORs for the highest versus lowest quartiles of usual BMI were 8.7 (95% CI 2.4–31.1) among non-smokers and 2.9 (95% CI 1.1–7.6) among current smokers, cigarette smoking being a significant effect modifier.

Lagergren *et al.* (1999a) studied 189 and 262 Swedish patients with oesophageal and cardia adenocarcinoma, respectively. Strong positive associations with oesophageal adenocarcinoma were observed for BMI above 25.6 kg/m^2 for men or 24.2 kg/m^2 for women relative to the lowest quartile (OR = 7.6; 95% CI 3.8–15.2), and for obesity (BMI above 30 kg/m^2) relative to BMI less than 22 kg/m^2 (OR = 16.2; 95% CI 6.3–41.4).

Discussion

In six out of eight reported case–control studies, an increased risk was observed with higher BMI, notably at high BMI values. The risk is higher for oesophageal adenocarcinoma than for cardia adenocarcinoma. No association has been reported between squamous cell carcinoma and BMI. The association between BMI and adenocarcinoma of the oesophagus and cardia is strong and seems not to be explained by bias or confounding.

An increased incidence of gastric reflux has been proposed as the underlying cause of the elevated risk of adenocarcinoma in persons with high BMI (Hagen *et al.*, 1987; Mercer *et al.*, 1987; Stene-Larsen *et al.*, 1988). Although the risk in one study (Lagergren *et al.*, 1999a) was independent of gastro-oesophageal reflux symptoms, support for this hypothesis comes from the observation that medications that lower oesophageal sphincter pressure, thereby increasing reflux, have been associated with oesophageal adenocarcinoma (Lagergren *et al.*, 2000).

Pancreatic cancer

Due to its high fatality, pancreatic cancer is one of the leading causes of cancer death in developed countries. Most pancreatic cancers derive from the exocrine component of the pancreas. Studies of migrants suggest that environmental factors influence the risk of pancreatic cancer; tobacco smoking is the single established cause (Ögren *et al.*, 1996). Studies of BMI and risk of pancreatic cancer with more than 100 cases are listed in Table 35.

Cohort studies

Only one cohort study out of four (Friedman & van den Eeden, 1993; Shibata *et al.*, 1994; Møller *et al.*, 1994; Ögren *et al.*, 1996) included more than 100 cases. In this exploratory nested case–control study in the San Francisco Bay area (Friedman & van den Eeden, 1993) within a large cohort of the Kaiser Permanente Medical Care Program, increased body weight measured at baseline was associated with somewhat higher pancreatic cancer risk (RR = 1.1; 95% CI 1.0–1.04). A unit increase in BMI

Table 34. Studies of body mass index and risk of adenocarcinoma of the oesophagus (AE) and of the gastric cardia (AC)

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend*	Adjustment for confounding	Comments
Cohort studies							
Tretli & Robsahm (1999), Norway	1963–89	M: 94 F: 25	Highest vs lowest (5)	AE: 2.4 (1.3–4.4) 1.6 (0.5–4.8)	No	Age, birth cohort, county of residence	Tuberculosis screening programme
Case–control studies							
Kabat *et al.* (1993), USA	1981–90	M:121 AE+AC	≥ 28 vs <22 (4)	0.8 (0.4–1.7)	No	Age, education, hospital, alcohol, smoking, dietary factors	Hospital-based
Brown *et al.* (1995), USA	1986–89	M:161 AE+AC	>26.6 vs <23.1 (4)	3.1 (1.8–5.3)	No	Age, area, liquor use, income, energy intake, smoking	Population-based
Vaughan *et al.* (1995), USA	1983–87	M+F: 131 AE M+F: 164 AC	Percentiles 90–100% vs 10–49%	2.5 (1.2–5.0) 1.6 (0.8–3.0)	Yes Yes	Age, gender, education, race, cigarette smoking, alcoho	Population-based
Zhang *et al.* (1996), USA	1992–94	M+F: 95 AE+AC	Not stated	AE+AC: 0.93 (0.83–1.03)	NE	Age, years of education, smoking, alcohol, total energy intake, sex, race, iron deficiciency, stomach ulcers, hypertension, Barrett's oesophagus	Hospital-based
Ji *et al.* (1997), China	1988–89	M:148 AC F: 37 AC	>22.2 vs <19.4 (4) >22.9 vs <19.5 (4)	3.0 (1.7–5.4) 1.4 (0.5–4.1)	Yes Yes	Age, education, income, cigarette smoking, alcohol, total energy intake, chronic gastric diseases	Population-based
Chow *et al.* (1998), USA	1993–95	M: 244 AE F: 48 AE M: 223 AC F: 38 AC	≥27.3 vs <23.1 (4) ≥27.4 vs <22.0 (4)	3.0 (1.7–5.0) 2.6 (0.8–8.5) 1.8 (1.1–2.9) 1.3 (0.4–4.2)	Yes Yes Yes No	Age, cigarette smoking geographic location, race, sex	Population-based
Lagergren *et al.* (1999a), Sweden	1995–97	M+F: 189 AE M+F: 262 AC	M: >25.6 vs <22.3 (4) F: >24.2 vs >21.1 (4) BMI 20 y before interview	AE: 7.6 (3.8–15.2) AC: 2.3 (1.5–3.6)	Yes Yes	Age, sex, tobacco smoking, socioeconomic status, reflux symptoms, energy intake, physical activity, fruit and vegetables	Population-based
Cheng *et al.* (2000), UK	1993–96	F: 68	BMI at age 20, ≥22.7 vs ≤19.5 (4)	AE: 6.0 (1.3–28.5)	Yes	Age, fruit consumption, breast-feeding, social class, no. of children	Population-based

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories

Table 35. Studies of body mass index and risk of pancreas cancer

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend*	Adjustment for confounding	Comments
Cohort studies							
Friedman & van den Eeden (1993), USA	1964–88, follow-up 1 day–24.1 years	M+F: 450	BMI (per unit increase), measured at inclusion	1.02 (1.00–1.04)	No	Age, cigarette smoking, race	Exploratory study, testing 779 characteristics
Case–control studies							
Bueno de Mesquita *et al.* (1990), The Netherlands	1984–88	M: 89 F: 79	> 27.9 vs < 23.0 (5) > 28.7 vs <21.6 (5) two years before diagnosis	0.88 (0.40–1.9) 1.1 (0.46–2.8)	No	10–year age group, response status, total smoking	Population-based
			> 27.9 vs <23.0 (5) > 28.7 vs <21.6 (5), maximum BMI ever attained	0.72 (not given) 0.89 (not given)	No		
Ghadirian *et al.* (1991), Canada	1984–88	M+F: 179	> 26.5 vs <21.1 (4)	0.88 (0.42–1.8)	No	Age, sex, response status, cigarette smoking	Population-based
Ji *et al.* (1996), China	1990–93	M: 255 F: 183	> 22.5 vs < 19.4 (4) > 23.2 vs < 19.4 (4) usual BMI	1.4 (0.91–2.1) 1.5 (0.85–2.5)	Yes No	Age, income, smoking, physical activity, response status, diabetes, vitamin C, total energy	Population-based
Silverman *et al.* (1998), USA	1986–89	M: 218 F: 213	> 27.2 vs < 23.1 (4) > 34.4 vs < 27.5 (4) usual adult BMI	1.5 (1.0–2.3) 1.5 (0.9–2.5)	Yes No	Age, race, study area, diabetes, cholecystectomy, cigarette smoking, alcohol, income (men), marital status (women)	Population-based

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories

was associated with an RR of 1.02 (95% CI 1.00–1.04). The studies of Ögren *et al.* (1996) and Møller *et al.* (1994), which included rather few cases, also found significant increased risk for pancreatic cancer in relation to high BMI.

Case–control studies

During 1984–88, a population-based case–control study of exocrine pancreas carcinoma was carried out in Utrecht, the Netherlands as part of the IARC SEARCH programme (Bueno de Mesquita *et al.*, 1990). The risk of pancreatic cancer in relation to high BMI suggested non-significant opposite effects for males and females, with reduced risk in men and increased risk in women for all quintiles of BMI two years before diagnosis, compared with the lowest quintile. In contrast, the highest BMI ever obtained was associated with non-significant reduced risks in both men and women.

Another participant in the SEARCH Collaborative Study Group carried out a case–control study in Montreal, Canada (Ghadirian *et al.*, 1991). No clear trend in risk of pancreatic cancer with increasing BMI was seen (OR = 0.88; 95% CI 0.42–1.8 for the highest versus lowest BMI quartiles).

In a case–control study in Shanghai, China (Ji *et al.*, 1996), interview data were obtained on weight during adulthood (usual weight) and at four different periods (ages 20–29, 30–44, 45–54 and ≥55 years). In both men and women, the highest quartile of usual BMI was associated with a non-significantly increased risk of pancreatic cancer, with the lowest quartile as reference category.

In a case–control study conducted in Atlanta, Detroit and New Jersey, USA, from 1986 to 1989, 436 patients and 2003 general population controls were interviewed (Silverman *et al.*, 1998). For both men and women, the highest quartile of BMI (≥27.2 and ≥34.4 kg/m^2, respectively) was associated with a 50% increase in risk of pancreatic cancer, compared with BMI 17.4–23.1 and BMI 20.5–27.5 kg/m^2, respectively. Blacks and whites experienced similar BMI-related risks.

Discussion

Only one exploratory cohort study and four case–control studies on the relationship between BMI and pancreatic cancer included 100 cases or more. Both lower and higher risks related to high BMI have been observed, with the studies finding an increased risk most often showing a dose–response effect. The highest risk was seen in the study in China, where the highest exposure category started at a rather low BMI compared with the other studies. All the case–control studies on pancreatic cancer were subject to bias because of a low participation rate among cases and use of information obtained from next-of-kin, due to the high mortality rate of this cancer.

Overall, the evidence is too limited to allow any firm conclusion to be drawn on the relationship between BMI and the risk of pancreatic cancer.

Cancer of the head and neck

Tobacco smoking and alcohol drinking account for over 90% of cancers of the oral cavity and pharynx in developed countries (IARC, 1986, 1988). Dietary factors (i.e., low consumption of fruit and vegetables and high intake of saturated fat (McLaughlin *et al.*, 1988) have also been related to risk. Several case–control studies on the association between weight and cancer of the head and neck have been reported, but no cohort studies (Table 36).

Case–control studies

An inverse association with weight and/or BMI was reported in four case–control studies on cancer of the oral cavity and pharynx in the USA (McLaughlin *et al.*, 1988; Marshall *et al.*, 1992; Day *et al.*, 1993; Kabat *et al.*, 1994), two in Italy (D'Avanzo *et al.*,1996a; Franceschi *et al.*, 2001), and one in China (Zheng *et al.*, 1993a). Two case–control studies in the USA (Muscat & Wynder, 1992) and Italy (D'Avanzo *et al.*, 1996a) showed a similar, but somewhat weaker, inverse association between BMI and laryngeal cancer.

The risk pattern according to BMI seems to be similar in men and women, as well as in whites and blacks. Conversely, smoking and, possibly, heavy alcohol drinking seem to modify the apparent adverse effect of leanness. Three studies included an assessment of BMI according to smoking status, two of which found that BMI was not significantly related to oral cancer risk among never-smokers of either sex (Kabat *et al.*, 1994; Franceschi *et al.*, 2001). An association between oral and laryngeal cancers and BMI was found by D'Avanzo *et al.* (1996a) among never-smokers (OR = 0.5; 95% CI 0.3–0.7), but was weaker than among current smokers.

Weight at cancer diagnosis, but before disease-related weight changes, was generally considered in these studies. However, McLaughlin *et al.* (1988) reported that BMI at age 20 years was unrelated to oral cancer incidence. Franceschi *et al.* (2001) observed that male cases of oral cancer had significantly lower BMI than control subjects also at ages 30 and 50 years.

Discussion

A low BMI has emerged consistently as a marker, possibly a relatively early one, of increased risk of cancer of the head and neck in eight case–control studies in the USA, Europe and China. In the three studies where it was possible to restrict the analysis of BMI to never-smokers, however, the inverse association with BMI, if any, was weak.

Testicular cancer

Testicular cancer incidence has increased markedly in recent years among many populations worldwide, coincident with increases in obesity. Obesity often reflects altered levels of

Table 36. Case–control studies of body mass index and risk of cancer of the head and neck

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend*	Adjustment for confounding	Comments
Oral cavity and pharynx							
McLaughlin *et al.* (1988), USA	1984–85	871	Highest vs lowest quartile	M: 0.5 F: 0.6	Yes No	Age, sex, smoking, alcohol	Population-based
Marshall *et al.* (1992), USA	1975–83	290	≥ 28 vs ≤ 23 (4)	0.4 (0.2–0.6)	Yes	Age, sex, education, smoking, alcohol	Population-based
Day *et al.* (1993), USA	1984–85	1065 (194 Blacks)	F: Weight/height$^{1.5}$ M: weight/height^{2} Highest vs lowest quartile	White: 0.6 Black: 0.3	Yes Yes	Age, sex, location, respondent, status, smoking, alcohol	Population-based
Zheng *et al.* (1993a), China	1989	404	≥26 vs ≤20 (4)	0.40 (0.23–0.69)	Yes	Age, sex, education, smoking, alcohol, inadequate dentition	Population-based
Kabat *et al.* (1994), USA	1977–90	M: 1097 F: 463	Highest vs lowest quartile	M: Current smokers: 0.3 (0.2–0.5) Never-smokers: 0.7 (0.3–1.7) F: Current smokers: 0.6 (0.3–1.1) Never-smokers: 0.6 (0.3–1.3)	Yes No No No	Age, sex, education, race, smoking, alcohol	Hospital-based
D'Avanzo *et al.* (1996a), Italy	1985–91	M: 462	M: ≥26.8 vs ≤ 22.6 (4)	0.2 (0.2–0.3)	Yes	Age, sex, education, smoking, alcohol, β-carotene intake	Hospital-based
Franceschi *et al.* (2001), Italy and Switzerland	1992–97	M: 638 F: 116	≥ 28.5 vs < 22.7 (5) >26.9 vs ≤ 23.8 (3)	M: 0.3 (0.2–0.4) F: 0.5 (0.2–1.1) Non-smokers: 0.8 (0.4–1.7)	Yes No No	Age, centre, physical activity, alcohol, smoking, intake of energy, fruit and vegetables	Hospital-based
Larynx							
Muscat & Wynder (1992), USA	1985–90	M: 194	Highest vs lowest quartile	0.2 (0.02–0.6)	NE	Age, education, smoking, alcohol	Hospital-based
D'Avanzo *et al.* (1996a), Italy	1985–91	M: 369	M: ≥26.8 vs ≤22.6 (4)	0.5 (0.3–0.7)	Yes	Age, sex, education, smoking, alcohol, β-carotene intake	Hospital-based

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories

estrogens and other sex hormones, which may be related to the risk of neoplasia of endocrine organs. Thus, obesity either early in life and/or later in life might affect testicular cancer risk. The five published studies are summarized in Table 37.

Cohort studies

In a large prospective study in Norway, a lower risk was observed among men with higher BMI as adults (RR = 0.70 for men with BMI of 20–25 kg/m^2 compared with below 20 kg/m^2) (Akre *et al.*, 2000). A marginally reduced risk was seen for men who were obese (RR = 0.73 above BMI 30 kg/m^2 compared with below 20 kg/m^2).

Case–control studies

Four case–control studies have focused on the association between weight and testicular cancer. A hospital-based case–control study including 259 cases (138 seminomas, 104 teratomas, 17 mixed histology) was conducted in England (Swerdlow *et al.*, 1989). Risk of testicular cancer was raised among men with a high BMI as adults, but not significantly, and there was no overall significant relationship. In a later population-based case–control study in England and Wales including 794 testicular cancer cases, no association with weight was observed (UK Testicular Cancer Study Group, 1994a). Similarly, a case–control study conducted in Canada including 510 men with testicular cancer aged 15–79 years found no association of BMI at age 21 years with increased risk (Gallagher *et al.*, 1995). In contrast, men with an adult BMI of 22–24 kg/m^2 were at lower risk (OR = 0.4; 95% CI 0.2–0.8) compared with those having BMI ≤ 21 kg/m^2 (Petridou *et al.*, 1997).

Discussion

Studies have reported either inverse associations between BMI and testicular cancer risk (Petridou *et al.*, 1997; Akre *et al.*, 2000) or no association (Swerdlow *et al.*, 1989; UK Testicular Cancer Study Group, 1994a; Gallagher *et al.*, 1995); no firm conclusion can be drawn on this relationship. Birth weight was not associated with increased testicular cancer risk in one case–control study (Sabroe & Olsen, 1998).

Cancer of the thyroid

Thyroid hormones are relevant to the growth and development of several body tissues, and weight is affected by hypo- and hyperthyroidism. An association between BMI (or weight gain) and thyroid cancer has been suggested by a number of case–control studies.

Case–control studies

Ron *et al.* (1987), in a study of thyroid cancer in Connecticut, USA, found an OR of 1.5 for women (but not men) in the highest BMI quartile at age 18 years and in adult life. Goodman *et al.* (1992), in a study from Hawaii, reported ORs of approximately 4.0 for men and 2.0 for women in the highest quartile of weight or BMI, and a significant direct association with weight and weight gain in women. In Shanghai, China, the ORs were 2.3 for the highest weight category and 2.0 for the highest level of weight gain; both estimates were significant (Preston-Martin *et al.*, 1993). In a study of 410 female cases and 574 control women in Washington State, USA, Rossing *et al.* (2000) reported an OR of 1.5 (95% CI 1.0–2.2) in women who weighed 185 pounds (84 kg) or more one year before diagnosis, compared with those who were lighter.

Dal Maso *et al.* (2000) carried out a pooled analysis of the relationship between anthropometric factors and thyroid cancer using individual data from 12 case–control studies (including those referred to above, except for Rossing *et al.*, 2000) conducted in the USA, Japan, China and Europe. A total of 2056 female and 417 male cases, 3358 female and 965 male controls were considered. Papillary carcinomas accounted for 78% of the thyroid cancers. ORs were derived by logistic regression, conditioning on age, A-bomb exposure (Japan) and study, and adjusting for radiotherapy.

Reported BMI at diagnosis was directly related to thyroid cancer risk for females in most studies, with a pooled OR of 1.2 (95% CI 1.0–1.4) for the highest tertile. The corresponding figure was 1.3 (95% CI 1.1–1.5) when the three Nordic studies were excluded. Similar to the finding for weight, no consistent association was observed in males (ORs 0.8 and 1.0 in subsequent tertiles). The pooled OR was 1.1 (95% CI 0.99–1.2). No consistent pattern of risk was observed for BMI between ages 17 and 20 years.

Discussion

A majority of the 13 case–control studies in the USA, China, Japan and Europe suggest a modest direct association between BMI and thyroid cancer risk in women. If such an association exists, it may be related to a potential association between thyroid tumours and steroid hormones or other endocrine factors. Overweight is related to increased estrogen levels in postmenopausal women (IARC,1999) and exogenous estrogens are weakly related to increased thyroid cancer risk (La Vecchia *et al.*, 1999a; Negri *et al.*, 1999). In the pooled analysis, however, the influence of weight or BMI was of similar magnitude in older postmenopausal women and in younger ones. Some association with weight or BMI may be due to more frequent examination of the thyroid gland in overweight young women, particularly in the USA.

Gall-bladder cancer

Very few studies have investigated the relationship between weight or BMI and the risk of gall-bladder cancer. Descriptive studies have suggested that gallstones and obesity are risk factors for gall-bladder cancer. Of the cohort and case–control studies reported to date, only one included more than 100 cases.

Table 37. Studies of body mass index and risk of testicular cancer

Author, date, study location	Study dates	No. of cases	BMI range contrasts (no. of categories)	Relative risk (95% CI)	Trend*	Adjustment for confounding	Comments
Cohort studies							
Akre *et al.* (2000), Norway	1963–90	553	20.0–24.9 vs < 20.0 (5)	0.7 (0.5–0.9)	NE	Age	General population
Case–control studies							
Swerdlow *et al.* UK	1977–81	254	≥ 30 vs 20–24 (5)	2.0 (0.82–4.7)	No	Age, region of residence	Hospital-based
UK Testicular Cancer Study Group (1994a), UK	1984–86	790	Weight > 89 kg vs <60 kg (5)	1.1 (0.66–1.9)	No	Age, cryptorchidism, inguinal hernia	Population-based
Gallagher *et al.* (1995), Canada	1980–85	487	Age 21 y: ≥ 28 vs < 21 (5)	1.1 (0.7–1.7)	No	Age, ethnic origin, inguinal hernia, undescended testis	Population-based
Petridou *et al.* (1997), Greece	1993–94	97	22–24 vs ≤21 (5)	0.4 (0.2–0.8)	No	Age	Population-based

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories

Cohort studies

In a cohort study on obese patients in Denmark, Møller *et al.* (1994) found a non-significant increased risk of gall-bladder cancer (RR = 1.4; 95% CI 0.9–2.1) in women.

Case–control studies

A study conducted in Mexico including 71 women and 13 men found a non-significant increased risk of gall-bladder cancer for higher BMI values (Strom *et al.*, 1995). In a large case–control study conducted within the IARC SEARCH programme, including 196 cases (44 men and 152 women) of gall-bladder cancer from five centres in Australia, Canada, the Netherlands and Poland (Zatonski *et al.*, 1997), higher BMI was associated with an elevated risk of gall-bladder cancer in females (OR = 2.1; 95% CI 1.2–3.8, for highest versus lowest quartiles), but not in males.

Discussion

Among the few reported studies, some have suggested a slight increased risk of gallbladder cancer related to a high BMI, especially for women. However, since only one study included more than 100 cases and this was the only one to control for potential risk factors such as age, alcohol drinking, tobacco smoking and socioeconomic status, the data remain inconclusive.

Malignant melanoma

Cohort studies

In one prospective study, BMI was associated with increased risk of malignant melanoma in men, while obese females were at lower risk compared with lean women (Thune *et al.*, 1993).

Case–control studies

No association was observed between BMI and malignant melanoma in a case–control study of 361 patients conducted in Canada (Gallagher *et al.*, 1985). This lack of association was supported in two other studies (Dubin *et al.*, 1986; Østerlind *et al.*, 1988), but not in a study of men and women combined, where a positive association with BMI was found (Kirkpatrick *et al.*, 1994).

Discussion

The results from the few studies conducted on malignant melanoma are inconsistent and do not allow any firm conclusion to be drawn on the relationship with BMI. BMI may influence sunbathing behaviour and hormonal factors, both of potential importance for development of skin cancer.

Cervical cancer

The international variation in cancer of the female reproductive system (breast, cervix uteri, corpus uteri and ovary) suggests certain common etiological factors. Overweight has been established as a risk factor for cancer of the corpus uteri (endometrial cancer; see above). However, few studies have focused on the association between cervical cancer and weight.

Cohort studies

The only cohort study identified included 271 cases of cervical cancer during 25 years of follow-up (Törnberg & Carstensen, 1994). No association with BMI was observed.

Case–control studies

Two small case–control studies have examined the association between weight and cervical cancer. A positive association with overweight was observed in a study including 39 cases in Italy (Parazzini *et al.*, 1988), but no association with BMI was found in a study in Germany (Sönnichsen *et al.*, 1990).

Discussion

Two case–control studies including less than 100 cases and one cohort study have been reported, and found either no association (Törnberg & Carstensen, 1994; Sönnichsen *et al.*, 1990) or a positive relationship (Parazzini *et al.*, 1988; Guo *et al.*, 1994) between cervical cancer and weight. Overall, the evidence is too limited to allow any conclusion on the relationship between BMI and risk of cervical cancer.

Other cancer sites

The Working Group was aware that certain other cancers (e.g., non-Hodgkin lymphoma, malignant myeloma, meningioma) have been studied in relation to weight. However, so few studies were identified for each cancer site that evaluation of the risks would be premature.

Population attributable risk

Overall, there is considerable evidence that overweight and obesity are associated with risk for some of the most common cancers. The proportion of any disease due to a risk factor in a population is determined by both the size of relative risk and the prevalence of the risk factor in the population. That proportion, often referred to as the population attributable risk (PAR), has been estimated by others for increased BMI in relation to many of the cancer sites reviewed here. Bergström *et al.* (2001) (Table 38) computed estimates of the PAR from overweight (BMI 25–29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) for selected cancers across countries of Europe, where about 50% of men and 35% of women are overweight, and 13% of men and 19% of women are obese. The risk estimates used in that analysis came from the authors' meta-analysis of the larger studies in the world literature, and are in line with those from the larger set of epidemiological studies included in the present review (see Tables 23–37). Because oesophageal cancer was not included in the analysis by Bergström *et al.* (2001), the PAR for oesophageal cancer due to overweight and obesity has been estimated here based on an RR of 2.0 for BMI over 25 kg/m^2 in Europe (see Table 34).

These PAR estimates are estimates that would apply to industrialized countries. However, the size of the PAR in any population will be dependent on the prevalence of elevated BMI in that population, which in some populations changes substantially over time. The prevalence of obesity continues to rise in many industrialized countries, and is also becoming a problem in many developing countries (see Chapter 2 and Popkin & Doak, 1998).

Physical activity

In view of the difficulty in measuring physical activity in a standardized manner, studies of the relationship between cancer and physical activity are described in some detail for the more important sites reviewed below.

Colorectal cancer

Occupational activity, leisure-time activities and participation in sports have been examined in a variety of populations to estimate the association between physical activity and colorectal cancer. Total activity and specific components of physical activity, such as level of intensity at which activities are performed, have been examined. Some studies have combined colon and rectal cancers (colo-rectal cancer), while others considered colon cancer separately and/or reported separate results for various subsites within the colorectal area. To clarify mechanisms and disease processes, some studies have looked at adenomas, the precursor lesion for most colorectal tumours. The results show that high levels of physical activity are consistently associated with reduced risk of colon cancer, although many of the studies that examined rectal tumours or colon and rectal cancers combined have yielded less consistent findings. However, this poorer consistency of associations for rectal cancers or colorectal cancer could stem in part from the less precise indicators of activity that were used.

The initial associations between physical activity and colon cancer were derived from observations that people involved in active occupations were less likely to develop colon cancer (Garabrant *et al.*, 1984; Vena *et al.*, 1987). Although physical activity was crudely categorized from occupational data in these studies, significant associations were detected and stimulated further examination of the associations, both for occupational activity and for other more comprehensive measures of total activity. Several studies have replicated the inverse association between job activity and colon or colorectal cancer (Fraser & Pearce, 1993; Hsing *et al.*, 1998b; Levi *et al.*, 1999a; Tavani *et al.*, 1999), while others failed to detect differences between cases and controls on the basis of reported occupation (White *et al.*, 1996; Le Marchand *et al.*, 1997; Slattery *et al.*, 1997a). Since occupational activity is tending to decrease for most people in developed societies, with leisure-time and recreational activities becoming a greater component of overall activity, it is likely that occupational activity is becoming a less sensitive discriminator of risk. For other populations where occupational activity remains more prevalent (Tavani *et al.*, 1999), occupational activity is still associated with colon cancer.

The findings of the cohort and case–control studies (Table 39) are remarkably similar, suggesting that the associations are real and perhaps causal. Some of the larger, more rigorously conducted studies are described below, and details of all studies with more than 100 cases are presented in the table.

Cohort studies

Lee *et al.* (1991) evaluated long-term activity in a cohort of 17 148 Harvard alumni aged 30–79 years. Those who were active at several assessments had half the risk of developing colon cancer compared with those who were not (RR = 0.50; 95% CI 0.27–0.93). Similar associations were detected for those who were highly active and those who were moderately active. Physical activity as assessed at any single time period did not show a protective effect.

In the US Male Health Professionals Study cohort of 47 723 men (Giovannucci *et al.*, 1995), there were 203 cases of colon cancer. Information was obtained by questionnaire on eight recreational activities and the amount of time spent per week on these activities. Physical activity was inversely associated with colon cancer after adjustment for age, BMI, diet and lifestyle factors (RR = 0.53; 95% CI 0.32–0.88, comparing high and low levels of activity).

A Norwegian cohort of 53 242 men and 28 274 women was followed for

Table 38. Estimates of population attributable risk due to overweight for selected cancer sites in developed countries (%)

	Attributable risk (%) for BMI > 25 vs <25 kg/m^2
Colon cancer[a]	11
Postmenopausal breast cancer[a]	9
Endometrial cancer[a]	39
Kidney cancer[a]	25
Oesophageal cancer[b]	37

[a] From Bergstrom *et al.* (2001)
[b] Based on RR of 2.0 for BMI > 25 (see Table 34)

about 16 years, yielding 263 and 99 cases of colon cancer in men and women, respectively (Thune & Lund, 1996). Both occupation and recreational activity were considered. High levels of total physical activity were protective for women (RR = 0.63; 95% CI 0.39–1.0) but not for men (RR = 0.97; 95% CI 0.63–1.5).

Associations between physical activity and colon cancer were reported for the US Nurses' Health Study cohort of 52 875 women who completed a physical activity questionnaire in 1986 (Martinez *et al.*, 1997). The questionnaire was the same as the one used in the Male Health Professionals Study and included questions on leisure and recreational activity only. In a multivariate analysis, physical activity was inversely associated with colon cancer (RR = 0.54; 95% CI 0.33–0.90) for those in the highest quintile of activity. Associations were slightly stronger for the distal colon (RR = 0.31; 95% CI 0.12–0.77) than for the proximal colon (RR = 0.77; 95% CI 0.38–1.6).

The Physicians' Health Study (Lee *et al.*, 1997a) included 21 807 US physicians who were followed for an average of 10.9 years. A total of 217 cases of colon cancer were detected during the follow-up. This study was a randomized trial of low-dose aspirin and β-carotene, in which a crude indicator of physical activity was available. No association between physical activity and colon cancer was seen (RR = 1.1; 95% CI 0.7–1.6 for the highest versus lowest levels of activity). It is unclear whether the intervention had any effect on the results.

Case–control studies

In a study by Slattery *et al.* (1988), participants were asked to report activity performed at leisure and at work two years before diagnosis or interview as the number of hours spent in light, moderate and intense activity. The study consisted of 204 female and 180 male controls and 119 female and 110 male colon cancer cases living in Utah, USA. Total physical activity was associated with a reduced risk of colon cancer for men; OR = 0.48; 95% CI 0.27–0.87 for women) after adjustment for diet, body size and age. Associations were present for intense activities (OR = 0.27; 95% CI 0.11–0.65) but not non-intense activities (OR = 1.2; 95% CI 0.68–2.3) among men. Both intense (OR = 0.55; 95% CI 0.23–1.3) and non-intense activities (OR = 0.53; 95% CI 0.29–0.95) were associated with colon cancer in women. However, since few women reported intense activities, estimates of association were imprecise. This study also showed significant interaction between dietary factors such as energy intake, protein and fat, and physical activity.

Three case–control studies reported in 1990 gave similar results to those of Slattery *et al.* (1988). Gerhardsson de Verdier *et al.* (1990a) assessed work and recreational activity among 452 colon cancer cases and 629 controls living in Stockholm, Sweden. People who reported being "very active" were at lower risk of developing colon cancer (OR = 0.6; 95% CI 0.3–1.0) relative to people who were sedentary, after adjustment for age, dietary factors, body size and gender. The associations were stronger for left colon cancer (OR = 0.32; 95% CI 0.14–0.71) than for right colon cancers (OR = 1.0; 95% CI 0.42–2.5).

Whittemore *et al.* (1990) examined associations between physical activity and colorectal cancer in Chinese living in North America and China. A total of 905 cases of colorectal cancer and 2488 controls were studied. Increased duration of exposure to a sedentary lifestyle was associated with increased risk of colorectal cancer. Inverse associations with colon cancer were detected for both job and lifestyle activities for men living in North America (OR = 0.4; 95% CI 0.2–0.9 for job activity; OR = 0.6; 95% CI 0.4–0.9 for lifestyle activity); women in North America reporting active lifestyles had a reduced risk of colon cancer (OR = 0.5; 95% CI 0.3–0.8). In China, activity was not associated with reduced risk of colon cancer in men (OR = 1.2; 95% CI 0.5–2.6), although it was protective among women (OR = 0.4; 95% CI 0.2–1.0).

A study of 715 histologically confirmed cases of colorectal cancer and 727 age- and sex-matched controls in Melbourne, Australia, did not find any significant association with physical activity (Kune *et al.*, 1990). People were classified as being totally inactive, not very active retired men and/or housewives or people in sedentary occupations; busy housewives; people on their feet most of the day doing moderate physical activity; or people performing strenuous activity such as manual labourers and athletes. This system of categorization may have led to misclassification.

Marcus *et al.* (1994) evaluated early adult physical activity in relation to colon cancer risk among women in Wisconsin, USA. The study population consisted of 536 cases and 2315 controls randomly selected from driver's license lists. Activity was reported for ages 14–22 years. After adjustment for age, family history of large bowel cancer, history of screening sigmoidoscopy and BMI, any strenuous physical activity during this time period was not associated with reduced risk of colon cancer (OR = 1.0; 95% CI 0.82–1.3).

A study by Longnecker *et al.* (1995) conducted in Los Angeles, California, USA, included data from 163 cases with right-sided colon cancer and 703 community controls. Questions about six specific leisure-time vigorous activities performed five years earlier were followed by an open-ended question about other forms of physical activity. People who reported two or more hours of vigorous activity per week were at reduced risk of colon cancer (OR = 0.57; 95% CI 0.33–0.97) after adjustment for smoking, income, race, family history of

Table 39. Studies of physical activity and risk of colorectal cancer

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Colorectal cancer, cohort studies							
Colorectum							
Wu *et al.* (1987), USA	1981–82	M: 58 F: 68	Time spent per day in activities (3)	0.62 (0.45–0.87)	Yes	Age, alcohol, smoking, BMI	Retirement community residents
Albanes *et al.* (1989), USA	1971–84	M: 88 F: 53	Recreational exercise (3)	M: 0.6 (0.1–2.5) F: 0.8 (0.1–5.0)	NE	Age	Age 25–74 years
Ballard-Barbash *et al.* (1990c), USA	1954–82	M: 73 F: 79	Physical activity index (3)	M: 0.6 (0.3–1.0) F: 0.9 (0.6–1.7)	No	Age	Age 30–62 years
Steenland *et al.* (1995), USA	1971–87	M: 94 F: 82	Current non-recreational activity (3)	M: 1.0 (0.5–2.0) F: 1.1 (0.5–2.5)	NE	Age, BMI, smoking, alcohol, income, diabetes, recreational activity	NHANES 1 study
Thune & Lund (1996), Norway	1972–91	M: 236 F: 99	Moderate to intense activity per week in recreation and occupation (3)	Recreational M: 1.3 (0.90–2.0) F: 0.84 (0.43–1.6) Occupational M 0.82 (0.59–1.1) F 0.69 (0.34–1.4)	No	Age, BMI, geographic region	
Will *et al.* (1998), USA	1959–72	M: 2722 F: 2819	Usual level of activity at work or play (3)	M: 0.7 (0.6–0.9) F: 0.9 (0.8–1.1)	NE	Age, race, BMI, education, family history of colon cancer, diet, aspirin, smoking, parity (F), pipe/cigar smoking (M)	
Colon cancer, cohort studies							
Gerhardsson *et al.* (1986), Sweden	1961–79	5100	Occupational titles by census (2)	0.8 (0.7–0.8)	NE	Age, population density, social class	Age 20–64 years
Vena *et al.* (1987), USA	1974–79	M: 6459 F: 604	Occupational activity from death certificate (4 or 3)	PMR = M: 89 (p<0.1) F: 80 (p<0.01)	NE	Age	Mortality not incidence
Gerhardsson *et al.* (1988), Sweden	1969–82	M: 99 F: 92	Work and leisure activity by intensity (2)	0.3 (0.1–0.8)	NE	Age, gender	Age > 44 years
Marti & Minder (1989), Switzerland	1979–82	1995	Occupational data based on census (3)	SMR=0.8	NE	Age	Mortality

Table 39 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Severson *et al.* (1989), USA	1965–86	M: 191	24-h index of all activities plus time sleeping (3 or 2) home/leisure:	Total: 0.71 (0.51–0.99) Moderate /intense vs sitting: 0.66 (0.49–0.88)	No	Age, BMI	Hawaii Japanese
Lee *et al.* (1991), USA	1962–88	M: 225	Recreational activity, stair climbing, blocks walked (3)	Activity in 1962/66/77; 0.85 (0.64–1.1)	No	Age	College alumni
Thun *et al.* (1992), USA	1982–88	M: 611 F: 539	Current recreational and occupational activity (4)	M: 0.6 (0.3–1.3) F: 0.9 (0.4–2.0)	No	Age, familial history, fat, fruits, vegetables and grains, BMI, NSAIDs	Mortality study
Chow *et al.* (1993), China	1980–84	M: 302 F: 936	Occupational data census (3)	M: 0.9 (0.7–1.0) F: 0.8 (0.7–1.0)	Yes	Age	Age > 30 years
Bostick *et al.* (1994), USA	1986–90	F: 212	Two physical activity questions (3)	0.95 (0.68–1.4)	No	Age, energy intake, height, vitamin E intake, vitamin A supplements	Age 55–69 years
Chow *et al.* (1994), Sweden	1961–79	M: 13940 F: 4892	Occupational titles by census	SIR Professional: M: 1.2 ($p < 0.01$) F: 1.0 Agricultural: M: 0.8 ($p < 0.01$) F: 0.9	NE	Age, region	
Giovannucci *et al.* (1995), USA	1987–92	M: 203	Moderate and vigorous leisure activity (5)	0.53 (0.32–0.88)	Yes	Age, BMI, family history, endoscopic screening, smoking, aspirin, diet	Age 40–75 years
Lee *et al.* (1997a), USA	1982–94	M: 217	Frequency of vigorous activity (4)	1.1 (0.7–1.6)	No	Age, obesity, alcohol, treatment	Age 40–84 years

Table 39 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Martinez *et al.* (1997), USA	1976–92	F: 161	Time per week in walking and selected moderate and vigorous activities (5)	0.54 (0.33–0.90)	Yes	Age, cigarette smoking, family history of colorectal cancer, BMI, hormone replacement therapy, aspirin, red meat, alcohol	Age 30–55 years
Hsing *et al.* (1998b), USA	1966–86	M: 120	Occupational history	Agricultural vs professional workers: M: 0.7 (0.3–1.4)	NE	Age, alcohol, physical activity	Mortality study
Rectal cancer, cohort studies							
Gerhardsson *et al.* (1986), Sweden	1961–79	4533	Occupational title by census (2)	0.9 (0.8–1.0)	NE	Age, population density, social class	Age 20–64 years
Thune & Lund (1996), Norway	1972–91	M: 170 F: 58	Recreational and occupational activity (3)	Recreational M: 0.98 (0.6–1.6) F: 1.5 (0.5–4.2) Occupational M: 1.0 (0.6–1.4) F: 0.88 (0.33–2.4)		Age, BMI, geographic region	Age 40–75 years
Colorectal cancer, case–control studies							
Peters *et al.* (1989), USA	1975–82	M: 147	Lifetime occupational titles (3)	1.1 (0.5–2.3)	No	Age, education	Population-based
Benito *et al.* (1990), Spain	1984–88	M: 151 F: 135	Current occupational activity (4)	0.7	Yes	Age	Population-based
Kune *et al.* (1990), Australia	1980–81	M: 388 F: 327	Recreational and occupational activity in previous 20 years (4)	M: 1.5 (0.8–2.7) F: 0.9 (0.3–2.8)	NE	Age, BMI, diet	Population-based
Le Marchand *et al.* (1997), USA	1987–91	M: 698 F: 494	Lifetime recreational activity and occupational activity (4)	Recreation M: 0.6 (0.4–0.8) F: 0.7 (0.5–1.1) Occupation M: 1.3 (0.9–1.9) F: 1.5 (0.9–2.3)	 Yes No No No	Age, family history of colorectal cancer, alcohol, cigarettes, eggs, dietary fibre, calcium, energy, BMI	Population-based

Table 39 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Levi *et al.* (1999a), Switzerland	1992–97	M: 142 F: 81	Occupational and recreational activity at different ages (3)	Occupation 15–19: 0.63 (0.40–1.0) 30–39: 0.44 (0.26–0.73) 50–59: 0.63 (0.37–1.1) Leisure 15–19: 0.97 (0.62–1.5) 30–39: 0.53 (0.33–0.86) 50–59: 0.54 (0.30–0.96)	Yes	Age, sex, education, alcohol and energy intake	Hospital-based
Tang *et al.* (1999), Taiwan	1992	M: 90 F: 70	Current non-ocupational activity (3)	M: 0.3 (0.1–0.8) F: 0.8 (0.3–1.9)	Yes	Age, energy intake, dietary fibre, vegetable, protein and water intake, smoking, alcohol	Hospital-based
Steindorf *et al.* (2000), Poland	1998–99	M+F: 180	Occupational activity (3) and three questions on recreational activity (3)	Occupational: 0.61 (0.29–1.3) Recreational: 0.45 (0.24–0.84)	NE	Age, energy intake, education	Hospital based
Colon cancer, case–control studies							
Garabrant *et al.* (1984), USA	1972–81	M: 2950	Occupational title (3)	0.55 (0.5–0.6)	Yes	Age	Population-based
Vena *et al.* (1987), USA	1957–65	M: 210	Lifetime occupation (4)	0.5 (p<0.001)	Yes	Age	Hospital-based
Slattery *et al.* (1988), USA	1979–83	M: 110 F: 119	Non-occupational and occupational activity by intensity (4)	Total M: 0.7 (0.4–1.3) F: 0.5 (0.3–0.9) Intense M: 0.3 (0.1–0.7) F: 0.6 (0.2–1.3)	Yes	Age, BMI, energy, fat, proteins	Population-based
Brownson *et al.* (1989), USA	1984–87	M: 1211	Occupational title from medical chart (3)	0.7 (0.5–1.0)	Yes	Age	Hospital-based
Fredriksson *et al.* (1989), Sweden	1980–83	M: 156 F: 156	Occupational history (5)	M: 0.8 (p<0.05) F: 0.7 (p<0.05)	NE	Age	Population-based

Table 39 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Gerhardsson de Verdier *et al.* (1990a), Sweden	1986–88	M+F: 352	Total work and leisure activity (3)	0.6 (0.3–1.0)	NE	Age, gender, BMI, energy, fat, protein, fibre, browning of meat	Population-based
Kato *et al.* (1990), Japan	1979–87	M: 756	Occupational codes (3)	0.6 (0.5–0.7)	Yes	Age	Hospital-based
Whittemore *et al.* (1990), Chinese in North America and China	1981–86	North America M: 179 F: 114 China M: 95 F: 78	Sedentary lifestyle (2)	North America M: 0.6 (0.4–0.9) F: 0.5 (0.3–0.8) China: M: 1.2 (0.5–2.6) F: 0.4 (0.2–1.0)	NE	Age	Population-based
Markowitz *et al.* (1992), USA	1985–90	M: 307	Occupational activity (3)	0.5 (0.3–0.8)	Yes	Age, race, geographical area, recreational activity at age 22–44 y	Hospital-based
Fraser & Pearce (1993), New Zealand	1972–80	M: 1651	Last occupation at registry (3)	0.8 (0.7–1.0)	NE	Age	Population-based
Marcus *et al.* (1994), USA	1990–91	F: 536	Participation in vigorous activity at ages 14–22 yrs (5)	≥ 7 times/wk: 0.46 (0.19–1.1) Any activity 1.0 (0.82–1.3)	No	Age, family history, screening, BMI	Population-based
Longnecker *et al.* (1995), USA	1986–88	M: 163	Occupational (3) and vigorous recreational activity (4)	Occupation 0.68 (0.31–1.5) Leisure 0.57 (0.33–0.97)	No Yes	BMI, family history, income race, smoking, alcohol, energy, fat, fibre, calcium	Population-based
White *et al.* (1996), USA	1985–89	M: 251 F: 193	Moderate/intense recreational activity (5); Occupational activity (3)	Total: M: 0.79 (0.48–1.3) F: 0.71 (0.39–1.3) Intense: M: 0.57 (0.35–0.92) F: 0.74 (0.43–1.3) Occupation: M: 0.84 (0.52–1.4) F: 0.89 (0.46–1.7)	No (M+F) Yes No No (M+F)	Age	Population-based

Table 39 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Slattery *et al.* (1997a,b), USA	1991–94	M: 1099 F: 894	Occupational (3), household and recreational activity 2 yrs before diagnosis, 10 and 20 yrs ago, by level of intensity (4 or 5)	Long-term vigorous: M: 0.61 (0.47–0.79) F: 0.63 (0.48–0.82) Total recent: M: 0.90 (0.70–1.2) F: 0.91 (0.67–1.2) Total recent vigorous: M: 0.71 (0.55–0.92) F: 0.88 (0.69–1.1) Occupation: M: 0.98 (0.77–1.2) F: 1.1 (0.87–1.4)	Yes	Age, BMI, energy, fibre, calcium, NSAIDs, family history of colorectal cancer	Population-based
Tavani *et al.* (1999), Italy	1991–96	M: 688 F: 537	Occupational activity at different ages (5)	15–19 yrs: M: 0.47 (0.31–0.71) F: 0.62 (0.44–0.89) 30–39 yrs: M: 0.64 (0.44–0.93) F: 0.49 (0.33–0.72) 50–59 yrs: M: 0.69 (0.45–1.0) F: 0.75 (0.47–1.2)	Yes	Age, energy, alcohol, education, centre	Hospital-based
Rectal cancer, case–control studies							
Garabrant *et al.* (1984), USA	1972–81	M: 1213	Occupational title (3)	1.0 (0.8–1.3)	No	Age	Population-based
Gerhardsson de Verdier *et al.* (1990a), Sweden	1986–88	M+F: 217	Total work and leisure activity (3)	1.0 (0.5–2.0)	NE	Age, BMI, calories, fat, protein fibre, browning of meat, gender	Population-based
Kato *et al.* (1990), Japan	1979–87	M: 753	Occupational codes (3)	0.8 (0.6–1.0)	Yes	Age	Hospital-based
Whittemore *et al.* (1990), Chinese in North America and China	1981–86	N: Amer. M: 105 F: 75 China M: 131 F: 128	Occupation and sedentary lifestyle (2)	North America: M: 0.67 (0.4–1.1) F: 0.53 (0.27–1.0) China: M: 1.4 (0.63–3.1) F: 1.4 (0.71–2.9)	NE	Age	Population-based

Table 39 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Markowitz *et al.* (1992), USA	1985–90	M: 133	Occupational activity (3)	0.6 (0.3–1.1)	No	Age, race, geographical area, recreational activity at age 22–44 y	Hospital-based
Fraser & Pearce (1993), New Zealand	1972–80	M: 1046	Last occupation at registry (3)	0.8 (0.7–1.0)	NE	Age	Population-based
Longnecker *et al.* (1995), USA	1986–88	M: 242	Occupational (3) and recreational activity (4)	Occupation: 0.99 (0.44–2.2) Leisure: 1.2 (0.70–2.0)	No	BMI, family history, income, race, smoking, alcohol energy, fat, fibre, calcium	Population-based
Le Marchand *et al.* (1997), USA	1987–91	M: 221 F: 129	Lifetime recreational activity and occupational activity (3)	Recreational M: 0.5, $p = 0.07$ F: 0.8, $p = 0.97$ Occupational: M: 0.8, $p = 0.49$ F: 1.1, $p = 0.87$	NE NE	Age, family history of colorectal cancer, alcohol, cigarettes, eggs, dietary fibre, calcium, energy, BMI	Population-based
Levi *et al.* (1999a), Switzerland	1992–97	M+F: 104	Occupational activity at 30–39 yrs (3)	0.49 (0.26–0.92)	No	Age, sex, education, alcohol and energy intake	Hospital-based
Tavani *et al.* (1999), Italy	1991–96	M: 435 F: 286	Occupational activity, at different ages (4)	Occupational 30–39 M: 1.3 (0.86–2.0) F: 0.88 (0.48–1.6)	No	Age, energy, alcohol, education, centre	Hospital-based

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories

colorectal cancer, BMI, alcohol intake and diet.

A study conducted in the Seattle–Puget Sound area of Washington State, USA (White *et al.*, 1996) included 251 male and 193 female cases and 233 male and 194 female controls identified by random-digit dialling. Physical activity was assessed by questions on frequency and duration of types of recreational and occupational activities during the 10-year period ending two years before diagnosis. After adjustment for age, a reduced risk of colon cancer was observed for men and women who reported two or more sessions of moderate- or high-intensity activity per week (OR = 0.70; 95% CI 0.49–1.0) relative to those without any activity. Further adjustment for sex, BMI, dietary factors and other health-related behaviours did not significantly modify the risk estimates. Associations were slightly stronger for men aged less than 55 years at the time of diagnosis (OR = 0.29; 95% CI 0.12–0.69 for ≥14.5 hours per week of moderate activity versus none).

A US multi-centre study of 1099 male and 894 female cases of colon cancer and 1290 male and 1120 female controls was conducted in the Kaiser Permanente Medical Care Program of northern California, an eight-county area of Utah and the Twin Cities area of Minnesota (Slattery *et al.*, 1997b). A questionnaire was used to assess recreational and occupational activity; activities performed at moderate and intense levels; and activities performed for the referent period of two years before diagnosis as well as activities performed 10 and 20 years ago. Long-term intense activity was the best predictor of colon cancer risk (OR = 0.61; 95% CI 0.47–0.79 for men; OR = 0.63; 95%CI 0.48–0.82 for women). Adjustment for other dietary and lifestyle factors did not alter the risk estimates. Interaction between BMI and total energy intake was observed, with physical activity having its greatest impact among those who having high energy intake and those who had higher BMI. Occupational activity was not associated with reduced risk of colon cancer (Slattery *et al.*, 1997a).

In a study in Hawaii among Japanese, Caucasian, Filipino and Chinese participants, 698 male and 494 female cases of newly diagnosed histologically confirmed large bowel cancer were matched to population-based controls (Le Marchand *et al.*, 1997). Lifetime physical activity was evaluated for recreational and occupational activity that included duration and intensity of activities performed. Reduced risk of colorectal cancer was observed for both men and women (men, OR = 0.6; 95%CI 0.4–0.8; women, OR = 0.7; 95% CI 0.5–1.1) after adjustment for age, BMI and lifestyle factors. As in the study by Slattery *et al.* (1997b), there was significant interaction between physical activity and BMI and energy intake for men.

Adenomas

Fewer studies have focused on adenomas than on adenocarcinomas. Associations for adenomas are less consistent between subgroups of the population than those observed in most studies of cancer (Neugut *et al.*, 1996; Little *et al.*, 1993). In some studies, associations with physical activity appear to be strongest and most consistent for large adenomas (Giovannucci *et al.*, 1995, 1996). In several studies, a 40% reduction in risk of colorectal adenomas has been observed (Sandler *et al.*, 1995; Giovannucci *et al.*, 1995, 1996; Lubin *et al.*,1997).

Discussion

As shown in Table 39, most studies have shown a consistent reduction in risk of colon cancer with increasing levels of activity; studies of rectal cancer and of colon and rectal cancers combined have given less consistent results. Consistent associations have been shown across diverse populations in Europe, Asia and America, with use of different indicators of physical activity. The magnitude of the risk reduction is consistently around 40% for colon cancer. It has been estimated from the results of a large multi-centre study in the USA that 13–14% of colon cancer may be attributable to physical inactivity (Slattery *et al.*, 1997a).

Several studies have shown a trend of decreasing risk of colon cancer with increasing levels of activity. Such a trend has been seen both for increasing intensity of activities and for increasing amounts of intense activity. The greatest reductions in colorectal cancer risk appear to be associated with level of intensity of activities performed (Slattery *et al.*, 1988; Marcus *et al.*, 1994; Longnecker *et al.*, 1995; White *et al.*, 1996; Slattery *et al.*, 1997b; Giovannucci *et al.*, 1995; Thune & Lund, 1996; Martinez *et al.*, 1997), total activity (Gerhardsson *et al.*, 1988; Slattery *et al.*, 1988; Severson *et al.*, 1989; Gerhardsson de Verdier *et al.*, 1990a) and/or long-term involvement in physical activity (Lee *et al.*, 1991; Slattery *et al.*, 1997b; Le Marchand *et al.*, 1997). The amount of activity to reduce risk is not clear, given the variety of methods used to assess activity, but it has been estimated that 30–60 minutes of more intense types of activities are needed to see the greatest effect in risk reduction (Slattery *et al.*, 1997a; White *et al.*, 1996; Marcus *et al.*, 1994; Wu *et al.*, 1987; Thune & Lund, 1996).

Overall, it appears that intense activity may be more protective against colon cancer than moderate levels of activity. While it is possible that intense activity stimulates biological mechanisms that moderate levels of activity do not, it is also possible that intense activities are reported better than moderate activities. In fact, data support the better long-term recall of intense activities than of moderate activities (Slattery & Jacobs, 1995). Misclassification of moderate activities would decrease ability to detect real associations.

Long-term involvement in activity appears to be an important predictor of colorectal cancer risk. It is not clear if those who are more active over long periods of time report their activity more accurately, or if long-term involvement in activity increases protection over a long period of time. Results of studies that show inverse associations between physical activity and adenomas provide support for a long-term benefit of physical activity.

As shown in Table 39, the studies have differed in the number and types of adjustment factors used to assess associations. Studies that have attempted to adjust for factors associated with risk of colon cancer, such as body size, diet, age, cigarette smoking status, use of aspirin and sunshine exposure, have not reported that the associations were confounded (Ballard-Barbash *et al.*, 1990c; Giovannucci *et al.*, 1995; Le Marchand *et al.*, 1997; Martinez *et al.*, 1997; Slattery *et al.*, 1997b). Also, given the consistency of the association between studies of colon cancer, it is likely that confounding contributes little to the observed associations. An evaluation of both cases and controls for reduced ability to exercise because of illness (Slattery *et al.* 1997a) suggests that cases do not report lower levels of past activities as a result of the tumour itself.

Studies to evaluate effect modification (Slattery *et al.*, 1997b, c) have shown that physical activity may most importantly reduce risk of colon cancer in the presence of high levels of energy intake, a high glycaemic index or large body size.

Breast cancer

Results for cohort and case–control studies with more than 100 cases are summarized in Table 40. More detailed descriptions are provided in the text of studies that had relatively good measures of physical activity, used incident cases, had good follow-up (cohort studies) or response rates (case–control studies) and adjusted for known and possible confounders of the association. No studies on physical activity in breast cancer among men have been reported.

Cohort studies

A few preliminary reports from cohort studies were not reviewed because the results were updated in a subsequent paper. This applies to the College Alumni Health Study (Paffenbarger *et al.*, 1987, updated by Sesso *et al.*, 1998), the National Health and Nutrition Examination I Survey (NHANES I) cohort (Albanes *et al.*, 1989, updated by Steenland *et al.*, 1995) and a Finnish cohort of teachers (Vihko *et al.*, 1992, updated by Pukkala *et al.*, 1993). The first report from the college graduates by Frisch *et al.* (1985) had only 69 cases, but in the later update by Wyshak and Frisch (2000) the size of the original cohort had decreased substantially, so that a 'healthy survivor' effect may have influenced the second follow-up results.

Of 14 separate cohort studies reviewed (Table 40), eight observed an inverse association between physical activity and breast cancer risk (Vena *et al.*, 1987; Zheng *et al.*, 1993b; Fraser & Shavlik, 1997; Thune *et al.*, 1997; Sesso *et al.*, 1998; Rockhill *et al.*, 1999; Moradi *et al.*, 1999; Wyshak & Frisch, 2000). The risk decreases ranged from 50–70% in the studies by Thune *et al.* (1997) and Sesso *et al.* (1998) to 20–30% in the studies by Vena *et al.* (1987), Zheng *et al.* (1993b), Fraser & Shavlik (1997), Rockhill *et al.* (1999) and Moradi *et al.* (1999). No association was found between physical activity in the follow-up study of the NHANES I cohort (Steenland *et al.*, 1995), in the Nurses' Health Study II cohort that included premenopausal women only (Rockhill *et al.*, 1998), in the Cancer Prevention II Study cohort (Calle *et al.*, 1998a) and in the Iowa Women's cohort study (Moore *et al.*, 2000a). Increased standardized incidence ratios for breast cancer were observed in the Finnish teachers cohort study for physical education and language teachers compared with the total Finnish population (Pukkala *et al.*, 1993). The follow-up of the Framingham Heart Study cohort also found an increased breast cancer risk among women who had the highest overall score on a physical activity index (Dorgan *et al.*, 1994). However, both of these studies that observed an increased risk of breast cancer had limitations in the methods used for assessment of physical activity.

Thune *et al.* (1997) studied a cohort of 25 624 Norwegian women from three population-based surveys conducted in 1974–78 and 1977–83. The women were aged 20–54 years at baseline and 351 cases were identified during the follow-up to 1994, with 100% follow-up achieved. A self-administered questionnaire was used to measure current occupational and recreational activity. Risk was statistically significantly reduced with higher occupational and recreational activity and evidence was seen for a dose–response relationship. The multivariate relative risk for women who were consistently active versus those who were sedentary for recreational activity was 0.6 (95% CI 0.4–1.0). For regularly exercising women aged less than 45 years at baseline, the risk was 0.38 (95% CI 0.19–0.79) and for women who were in the lowest BMI tertile, the risk for recreational activity was 0.3 (95% CI 0.1–0.7). Risk reductions were found for both pre- and postmenopausal women, but the associations were stronger and statistically significant for premenopausal women.

Rockhill *et al.* (1998) analysed physical activity and breast cancer in the Nurses' Health Study II cohort of 116 671 nurses aged 25–42 years (mostly premenopausal) in 1989 at baseline, who were followed up for six years. No association with recreational activity performed during late adolescence or in the recent past was found.

Table 40. Studies of physical activity and risk of breast cancer

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Cohort studies							
Vena *et al.* (1987), USA	1974–79	791	Usual lifetime occupational activity from death certificate (3)	PMR = 0.85, $p < 0.05$	NE	Age	Mortality study
Pukkala *et al.* (1993), Finland	1967–91	228	Current occupational title	SIR (vs general population) for: Physical activity teachers: 1.4 (1.0–1.9) Language teachers: 1.5 (1.3–1.7)	NE	Age	Based on national incidence figures
Zheng *et al.* (1993b), China	1980–84	2736	Current occupational activity from job title and index of sitting and energy expenditure (3)	SIR = 0.79, $p<0.01$	Yes	Age	Based on occupational data on census
Dorgan *et al.* (1994), USA	1954–88	117	Index of all types of physical activity performed in a day (4)	1.6 (0.9–2.9)	Yes	Age, age at FFTP, parity, menopausal status, alcohol intake, education, occupation	
Steenland *et al.* (1995), USA	1971–87	163	Current recreational and non-recreational activity (3)	1.1 (0.6–2.0)	NE	Age, BMI, smoking, alcohol, income, diabetes, menopausal status, recreational activity	NHANES I study
Fraser & Shavlik (1997), USA	1976–82	218	Current vigorous recreational and occupational activity (2)	0.7 (0.5–0.9)	NE	Age, age at FFTP, oral contraceptive and hormone replacement therapy use, family history, benign breast disease, energy and fat intake	Seventh-Day Adventists
Thune *et al.* (1997), Norway	1974–94	351	Current recreational (3) and occupational (4) activity	R: 0.6 (0.4–1.0) 0: 0.5 (0.3–0.9)	Yes	Age at entry, parity, BMI, height, county of residence	Age 20–54 years

Table 40 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Calle *et al.* (1998a), USA	1982–91	1780	Usual lifetime occupational activity	Housewives vs administratives: 1.1 (0.8–1.3)	NE	Age, age at menarche, age at FFTP, age at menopause, parity, BMI, benign breast disease, family history, oral contraceptive use, hormone replacement therapy use, smoking, alcohol, education, race, exercise	Mortality study
Rockhill *et al.* (1998), USA	1989–95	372	Recent recreational vigorous activity	1.1 (0.8–1.6)	No	Age, age at menarche, age at FFTP, parity, BMI, height, benign breast disease, family history, oral contraceptive use, alcohol consumption	Age 25–42 years
Sesso *et al.* (1998), USA	1962–93	109	Physical activity index composed of of current recreational activity, blocks walked, stairs climbed (3)	0.7 (0.5–1.1)	Yes	Age, BMI	University alumnae
Moradi *et al.* (1999), Sweden	1960–89	51520	Current occupational titles classified by intensity (4)	0.9 (0.8–1.0)	No	Age in five-year intervals, place of residence, calendar year of follow-up, socio-economic status	Three overlapping cohorts from national census
Rockhill *et al.* (1999), USA	1976–92	3137	Current recreational activity (5)	0.8 (0.7–1.0)	Yes	Age, age at menarche, age at FFTP, parity, BMI at age 18, height menopausal status/ use of hormone replacement therapy, benign breast disease, family history, oral contraceptive use in premenopausal models	Age 30–55 years
Moore *et al.* (2000a), USA	1986–97	1362	Current recreational activity (4)	0.9 (0.8–1.0)	No	Age, age at menopause, age at FFTP, BMI at age 18 y, education, family history, estrogen use	Age 55–69 years
Wyshak & Frisch (2000), USA	1981–96	175	Recreational activity in college (2)	0.6 (0.4–0.8)	NE	Age, parity, oral contraceptive and hormone replacement therapy use, family history, current exercise, smoking, per cent body fat	College alumnae

Table 40 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Case–control studies							
Dosemeci *et al.* (1993), Turkey	1979–84	241	Occupational titles to estimate average energy expenditure and sitting time over lifetime (2)	Energy: 0.7 (0.2–3.4) Sitting time: 1.0 (0.4–2.5)	No	Age, smoking and socio-economic status	Hospital-based
Bernstein *et al.* (1994), USA	1983–89	545	Lifetime recreational activity of at least 2h/wk (4)	Current activity 0.4 (0.3–0.6)	Yes	Age, age at menarche, age at FFTP, number of FFTPs, breastfeeding, oral contra-ceptive use, family history, BMI	Population-based age <40 years
Friedenreich & Rohan (1995), Australia	1982–84	444	Current recreational activity converted into kcal/wk expended (4)	0.7 (0.5–1.1)	No	Age, BMI and energy intake	Population-based
Hirose *et al.* (1995), Japan	1988–92	1063	Current recreational activity (3)	Premenopausal: 0.7 (0.6–1.0) Postmenopausal: 0.7 (0.5–1.0)	Yes	Age, age at menarche, age at FFTP, breastfeeding, BMI, height, smoking, alcohol intake, some dietary compo-nents (e.g., meats, vegetables)	Hospital-based
Mittendorf *et al.* (1995), USA	1988–91	6888	Strenuous recreational activity at ages 14–18 and 18–22 yrs (4)	0.5 (0.4–0.7)	Yes	Age, state, age at menarche, age at FFTP, parity, age at menopause, menopausal status, type of menopause, family history, benign breast disease, BMI, alcohol intake, interaction of BMI and meno-pausal status	Population-based
Taioli *et al.* (1995), USA	1987–90	617	Strenuous recreational activity at different ages (2)	15–21: 1.0 (0.6–1.8)	NE	Age, age at menarche, parity, education, BMI	Hospital-based controls

Table 40 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Coogan *et al.* (1996), USA	1988–91	6835	Usual lifetime occupational title	Administrative support occupation: 1.2 (1.1–1.2)	NE	Age, age at menarche, age at FFTP, parity, lactation, BMI, benign breast disease, family history, menopausal status, alcohol consumption, state education	Population-based All other occupation categories not associated with breast cancer Secondary analysis of Mittendorf *et al.* (1995)
D'Avanzo *et al.* (1996b), Italy	1991–94	2569	Occupational and recreational activity at different ages (5)	15–19 years: R: 1.0 (0.8–1.2) O: 0.8 (0.5–1.4) 30–39 years: R: 0.8 (0.6–1.1) O: 0.6 (0.4–1.0) 50–59 years: R: 0.7 0.4–1.1) O: 0.8 (0.4–1.5)	Yes	Age, age at menarche, age at FFTP, parity, age at menopause, menopausal status family history, benign breast disease, BMI, smoking, energy intake, education, centre	Hospital-based
McTiernan *et al.* (1996), USA	1988–90	537	Recreational activity 2 years before interview (3)	All women: 0.6 (0.4–1.0) Postmenopausal: 0.6 (0.3–0.9)	Yes	Age and education	Population-based
Chen *et al.* (1997), USA	1983–90	747	Recreational activity at ages 12–21 and 2 years before interview (5)	Two years before: 0.9 (0.7–1.2) 12–21 years: 1.1 (0.8–1.7)	No	Age	Population-based
Coogan *et al.* (1997), USA	1988–91	4863	Usual lifetime occupational activity (4)	0.8 (0.6–1.1)	Yes	Age, age at menarche, age at FFTP, menopausal status family history, benign breast disease, BMI, education, and alcohol intake, state, recreational activity at age 14–22 y	Population-based Secondary analysis of Mittendorf *et al.* (1995)
Hu *et al.* (1997), Japan	1989–93	157	Recreational activity in adolescence and in twenties (3)	Adolescence: Premenopausal: 0.7 (0.4–1.4)	No	Age	Population-based

Table 40 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Hu *et al.* (contd)				Postmenopausal: 1.4 (0.6–3.1) Twenties: Premenopausal: 1.0 (0.5–1.9) Postmenopausal: 0.5 (0.2–1.5)			
Gammon *et al.* (1998), USA	1990–92	1647	Recreational activity at ages 12–13, 20 and yr before interview (4)	12–13 years: 1.0 (0.8–1.2) 20 years: 1.1 (0.9–1.4) Year before interview: 1.1 (0.9–1.4)	No	Age, centre, age at menarche, age at FFTP, parity, lactation, abortions, miscarriages, menopausal status, marital status, education, family income race, BMI at age 20 y and adulthood, oral contraceptive and hormone replacement therapy use, alcohol, smoking, energy intake in past year, history of breast biopsy, family history	Population-based
Mezzetti *et al.* (1998), Italy	1991–94	2569	Occupational title at different ages (3)	30–39 years All women 0.7 (0.5–0.9) Premenopausal: 0.7 (0.5–1.1) Postmenopausal: 0.6 (0.4–0.9)	Yes	Age, centre, β-carotene, vitamin E, alcohol, BMI, energy intake, education, menopausal status	Hospital-based Re-analysis of D'Avanzo *et al.* (1996b)
Ueji *et al.* (1998), Japan	1990–97	139	Lifetime recreational activity (3) and most representative lifetime occupational activity (4)	Recreational activity: 0.4 (0.2–0.7) Occupational activity: 0.6 (0.3–1.1)	Yes No	Age, age at menarche, age at FFTP, menopausal status, parity, BMI, height, family history, education	Population-based
Carpenter *et al.*, (1999), USA	1987–89	1123	Lifetime recreational activity of at least 2 h/wk (3)	0.6 (0.4–0.8)	Yes	Age, age at menarche, age at FFTP, age a menopause, BMI family history, interviewer	Population-based Age 55–64 yrs

Table 40 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Coogan & Aschengrau (1999), USA	1983–86	233	Lifetime occupational activity (3)	0.9 (0.4–1.9)	No	Age, vital status, education, total duration of work	Population-based
Levi *et al.* (1999b) Switzerland	1993–98	246	Recreational and occupational activity at different ages (3)	Recreational activity: 15–19 yrs: 0.4 (0.3–0.7) 30–39 yrs: 0.5 (0.3–0.8) 50–59 yrs: 0.4 (0.2–0.8) Occupational activity: 15–19 yrs: 0.6 (0.4–1.0) 30–39 yrs: 0.5 (0.3–1.0) 50–59 yrs: 0.7 (0.4–1.3)	Yes	Age, age at menarche, age at FFTP, age at menopause, parity, menopausal status, benign breast disease, family history, energy intake, education	Hospital-based
Marcus *et al.* (1999), USA	1993–96	527 white and 337 African-American	Recreational and household activity at age 12 converted into summary measure (5)	0.6 (0.3–1.1)	No	Age at diagnosis, race, sampling design	Population-based
Moradi *et al.* (2000a), Sweden	1993–95	2838	Childhood (< 18 yrs) and adult (18–30 yrs) and current recreational activity (4)	Childhood: 1.0 (0.9–1.3) 18–30 yrs: 0.9 (0.8–1.1) Recent: 0.8 (0.7–0.9)	No No Yes	Age, age at menarche, parity, age at FFTP, age at menopause, BMI, height, hormone replacement therapy use,l oral contraceptive use	Population-based
Shoff *et al.* (2000), USA	1988–91	4614	Strenuous recreational activity at ages 14–18 and 18–22 yrs (4)	0.6 (0.4–0.8)	Yes	Age, age at menarche, age at FFTP, parity, age at menopause, BMI at age 18, family history, education	Population-based Secondary analysis of Mittendorf *et al.* (1995)
Verloop *et al.* (2000), Netherlands	1986–89	918	Lifetime recreational activity and title of longest job held (4)	0.6 (0.4–0.8)	NE	Age, education, family history	Population-based

Table 40 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Friedenreich *et al.* (2001a, b, c), Canada	1995–97	1233	Lifetime occupational, household, recreational activity (4)	Premenopausal women: 1.1 (0.7–1.6) Postmenopausal women: 0.7 (0.5–0.9)	No Yes	Age, hormone replacement therapy use, history of benign breast disease, family history, alcohol, smoking, waist/hip ratio, education	Population-based

PMR, proportional mortality ratio, OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio; FFTP, first full-term pregnancy; BMI, body mass index; MET, metabolic equivalent

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories

Rockhill *et al.* (1999) reported on the Nurses' Health Study I cohort of 121 701 women aged 30–55 years in 1976. Between 1980, when physical activity data were first collected and 1996, 3137 women were diagnosed with breast cancer, with 94% follow-up achieved. Breast cancer risks were slightly decreased among women who reported moderate or vigorous recreational activity levels compared with women who had low activity levels. The associations were nearly identical for pre- and postmenopausal women and there was no statistical interaction between menopausal status and cumulative average adult physical activity.

In the Iowa Women's Health Study, 37 105 postmenopausal study subjects aged 55–69 years at baseline in 1986 were followed to 1997, at which time 1380 women were diagnosed with breast cancer, with 79% follow-up (Moore *et al.*, 2000a). A self-administered questionnaire was used to measure current recreational activity at baseline and no follow-up assessments were made. No effect of physical activity on breast cancer risk was found.

Case–control studies

Several publications on different aspects of the certain case–control studies have been published. Thus, D'Avanzo *et al.* (1996b) first published results from a multi-centre case–control study in Italy, later extended by Mezzetti *et al.* (1998). Mittendorf *et al.* (1995) published the first results on recreational activity from a multi-centre case–control study conducted in four US states. Two subsequent publications from this study considered risk by occupation (Coogan *et al.*, 1996) and by occupational activity (Coogan *et al.*, 1997). The most recent publication from this study examined the effect of body size, weight change and early-life physical activity on risk of postmenopausal breast cancer (Shoff *et al.*, 2000). Bernstein *et al.* (1994) published data from a case–control study of women up to age 40 years and Carpenter *et al.* (1999) published data from another case–control study in California of women aged 55–64 years. The data from these two case–control studies were combined into a subsequent analysis by Enger *et al.* (2000) that examined the influence of body size, physical activity and breast cancer hormone receptor status on breast cancer risk.

Of 19 separate case–control studies (Table 40) that have reported data on physical activity and breast cancer risk, 14 found an inverse association (Bernstein *et al.*, 1994; Friedenreich & Rohan, 1995; Hirose *et al.*, 1995; Mittendorf *et al.*, 1995; D'Avanzo *et al.*, 1996b; McTiernan *et al.*, 1996; Hu *et al.*, 1997; Ueji *et al.*, 1998; Carpenter *et al.*, 1999; Levi *et al.*, 1999b; Marcus *et al.*, 1999; Moradi *et al.*, 2000a; Verloop *et al.*, 2000; Friedenreich *et al.*, 2001a, b, c). The papers from two population-based case–control studies in California among premenopausal women (Bernstein *et al.*, 1994) and postmenopausal women (Carpenter *et al.*, 1999) and the further stratified analyses of these data by BMI and hormone receptor status (Enger *et al.*, 2000) all reported strong risk reductions ranging from 40 to 60%. The risk reductions were even greater among certain subgroups of the study populations; for example, parous premenopausal women had a risk of 0.3 (95% CI 0.2–0.5) (Bernstein *et al.*, 1994).

Equally strong risk reductions were reported by Mittendorf *et al.* (1995) for recreational activity during adolescence and early adulthood. The subsequent analyses of the occupational data from this study found either no association with occupational title (Coogan *et al.*, 1996) or a decreased risk for usual occupational activity performed over lifetime (Coogan *et al.*, 1997). A further stratified analysis of recreational activity in early life (Shoff *et al.*, 2000) on this data-set confirmed the initial findings by Mittendorf *et al.* (1995).

Similarly, strong breast cancer risk decreases were observed for occupational and recreational activity performed during three time periods in life in the study by D'Avanzo *et al.* (1996b). These were confirmed in additional analyses of these data by Mezzetti *et al.* (1998), who presented only the occupational activity data for women at age 30–39 years, but provided more stratified analyses by menopausal status. McTiernan *et al.* (1996) observed strong risk reductions for recreational activity performed between adolescence and early adulthood. Likewise, particularly strong risk decreases have been noted for lifetime recreational activity (Ueji *et al.*, 1998) and for recreational and occupational activity at different time periods of life (Levi *et al.*, 1999b). Strong risk reductions were also found by Friedenreich *et al.* (2001a, b, c) for lifetime total physical activity, with the greatest reductions noted for occupational (0.59; 95% CI 0.44–0.81) and household activity (0.57; 95% CI 0.41–0.79) after menopause.

Bernstein *et al.* (1994) conducted a population-based case–control study among 545 cases and matched neighbourhood controls in California, USA. An interview-administered questionnaire was used to measure lifetime recreational activity in premenopausal women who were aged 40 years or less at the time of the interview. The initial study sample of 744 pairs was reduced to 545 pairs when the the method for recording physical activity was changed during the study. The response rate for the original sample of 744 cases was 78.4% and was not estimated for the controls because of the complex sampling strategy used to identify eligible controls. A statistically significant decrease in risk was found for women who performed 3.8 hours per week of recreational activity versus those who did none (OR = 0.4; 95% CI 0.3–0.6). The risk reduction was even stronger among physically active than among inactive parous women (OR = 0.28; 95% CI 0.16–0.50). Evidence of

a dose–response effect was found. Adjustment for confounding and examination of effect modification were performed, but no data on dietary intake were available.

Carpenter *et al.* (1999) conducted a similar case–control study in California, USA, using the same recruitment and data collection methods as Bernstein *et al.* (1994). A total of 1579 cases (69% of eligible patients) and 1506 controls were interviewed; the analysis was restricted to 1123 cases and 904 controls who were postmenopausal. The subjects were 55–64 years old at the interview. The response rate for cases was 67% and for controls was not estimated. Significantly decreased risks of breast cancer were found for women who performed 17.6 MET-hours per week or more of recreational activity compared with those who did none (OR = 0.6; 95% CI 0.4–0.8), for women who exercised for four hours per week for at least 12 years (OR = 0.71; 95% CI 0.52–0.96) and for those who exercised vigorously during the most recent 10 years (OR = 0.71; 95% CI 0.48–1.1). Risk reductions were also stronger among women who had less than 17% change in body weight during adulthood. No adjustment for dietary intake was possible. A dose–response effect was seen.

Mittendorf *et al.* (1995) conducted a multi-centre population-based case–control study in the USA among women aged 17–74 years. A total of 6888 cases and 9539 controls were included. Response rates were 81% for cases and 84% for controls. A telephone interview was used to assess strenuous recreational activity at ages 14–18 and 18–22 years. A statistically significant decreased risk was associated with strenuous versus no strenuous recreational activity in the total study population (OR = 0.5; 95% CI 0.4–0.7). This risk reduction was greater among women over 40 years of age than those under 40 and no effect modification by parity or menopausal status was found. A dose–response effect was seen. Full adjustment for confounding was made, although no data on dietary intake were available.

D'Avanzo *et al.* (1996b) conducted a multi-centre hospital-based case–control study in Italy in 1991–94 with women aged 23–74 years at interview. A total of 2569 cases and 2588 non-cancer controls were included and over 95% response rates were obtained. An interview-administered questionnaire was used to assess occupational and recreational activity at ages 15–19, 30–39 and 50–59 years. Non-significant decreased risks of breast cancer were found for activity performed at most of these time periods, except for occupational activity between ages 30–39 years, for which a risk of 0.6 (95% CI 0.4–1.0) was estimated. Evidence for a dose–response effect was found. Detailed adjustment for confounding was performed. Mezzetti *et al.* (1998) further analysed the data on occupational activity at age 30–39 years and found somewhat stronger risk reductions among postmenopausal women, for whom the risk was 0.6 (95% CI 0.4–0.9), but no effect modification on menopausal status was seen.

McTiernan *et al.* (1996) conducted a population-based case–control study in the state of Washington, USA, in 1988–90 among women aged 50–64 years at baseline. The study included 537 cases (81% of eligible) and 492 controls (73% of eligible). An interview-administered questionnaire was used to assess recreational activity performed between ages 12–21 years and two years before the interview. A borderline statistically significant decreased risk was found among women who performed high-intensity exercise during adulthood (OR = 0.6; 95% CI 0.4–1.0) compared with those who did no exercise. The effects were somewhat stronger for postmenopausal women (≥ 55 years of age only), for whom the risk was 0.6 (95% CI 0.3–0.9) among those who spent at least three hours weekly doing high-intensity exercise compared with those who did none. Evidence for a dose–response effect was found and full adjustment was made for confounding.

A similar population-based case–control study conducted by Chen *et al.* (1997) in the state of Washington, USA, in 1983–90 used the same population sampling and data collection methods as were used by McTiernan *et al.* (1996). This study included premenopausal women aged 21–45 years at the time of the interview. No effect of physical activity was found; adjustment for age only was performed, although several other factors were considered with the exception of dietary intake. In the studies by Chen *et al.* (1997) and McTiernan *et al.* (1996) and the two cohort studies by Rockhill *et al.* (1998, 1999), the same study methods were used and all four found no effect of physical activity among premenopausal women but a risk reduction among postmenopausal study subjects.

Another multi-centre population-based case–control study conducted by Gammon *et al.* (1998) in the USA, with 1668 cases (86% of eligible) and 3173 controls (79% of eligible) and similar study methods to Chen *et al.* (1997), also found no effect of physical activity on breast cancer risk. The study subjects were premenopausal women under 45 years of age who reported the frequency of recreational activity at ages 12–13 and 20 years and in the preceding year. Detailed adjustment was made for all confounders.

A population-based case–control study by Marcus *et al.* (1999) in North Carolina, USA, included 527 white and 337 African American cases (77% of eligible) and 790 (68% of eligible) controls. An interview-administered questionnaire was used to assess recreational and household activity at age 12 years. Some evidence of risk reduction was found for the different summary measures of activity used, but no dose–response effect was detected. Control for confounding was made for

most risk factors with the exception of dietary intake.

Verloop *et al.* (2000) conducted a population-based case–control study that included women aged 20–54 years in four regions of the Netherlands. A total of 918 case–control pairs were studied, with 60% and 72% response rates for cases and controls respectively. An interview-administered questionnaire was used to assess lifetime recreational activity and the title of the longest-held job. Several measures of physical activity were reported and most of these were associated with statistically significant risk reductions for breast cancer. For women who maintained recreational activity throughout their lifetime, the risk was 0.70 (95% CI 0.56–0.88) and when recreational and occupational activities were combined into one measure, women who were in the highest versus the lowest category had a risk of 0.58 (95% CI 0.42–0.82). Adjustment was made for risk factors except dietary intake. Effect modification by several other factors was explored and greater risk decreases were found among women who were parous, who ever had benign breast disease, who were leaner (lowest tertile of BMI) or who had a first-degree family history of breast cancer.

Moradi *et al.* (2000a) conducted a population-based case–control study in Sweden of women aged 50–74 years. The sample included 2838 cases (71% of original sample) and 3108 controls (76% of original sample). Recreational activity during childhood, early adulthood and current activity was assessed by questionnaire and occupational status in each decade between 1960 and 1990 was obtained from Swedish census data. A statistically significant risk reduction was observed for women who were the most active in combined recreational and occupational activities compared with the least active (OR = 0.32; 95% CI 0.13–0.76). When each type of activity was considered separately, slight decreases in risk of breast cancer were observed among the highest activity categories. Effect modification by BMI, parity and hormone replacement therapy was found. Greater postmenopausal breast cancer risk reductions were observed in association with occupational activity for nulliparous women and for leaner women (lowest tertile of BMI) who never used hormone replacement therapy. There was also evidence for a dose–response effect and adjustment for all confounders, except dietary intake, was performed.

Friedenreich *et al.* (2001a, b, c) conducted a population-based case–control study of women aged up to 84 years in Canada. The sample included 1233 cases (78% of eligible) and 1237 (56% of eligible). An interview-administered questionnaire was used to obtain lifetime physical activity patterns including all types of physical activity (i.e., occupational, household and recreational activity) from childhood until the reference year and all parameters of activity (i.e., frequency, intensity and duration). A 30% decreased risk of breast cancer was found for high total lifetime activity and even greater risk reductions (OR = 0.6; 95% CI 0.4–0.8) were observed for both occupational and household activity after menopause. The risk decreases were observed for postmenopausal women only, with no associations found for premenopausal women. Risk reductions were also noted for non-drinkers, non-smokers and nulliparous women. The reductions were particularly strong for activity done after menopause. In terms of patterns of activity, the greatest reductions were observed for activity sustained throughout lifetime and for activity done between menopause and the reference year. There was no linear association between intensity of activity and breast cancer risk, with the most notable risk reductions occurring for moderate-intensity activity. This was the first study that examined all types of activity and all parameters of activity throughout women's lifetimes.

Discussion

Results regarding the association between physical activity and breast cancer have been fairly consistent, since 22 of the 33 separate studies (eight of the 14 cohort studies and in 14 of 19 case–control studies) have found inverse associations among the most physically active participants compared with the least active. The decrease in risk of breast cancer was, on average, about 20–40%, with some studies observing up to 70% risk reductions. Evidence for a linear trend in decreasing risk of breast cancer with increasing activity was evident in the majority of the studies that examined the dose–response relationship. These associations were observed for both occupational and recreational activity, among pre- and postmenopausal women, for activity measured at different time periods in life and for different levels of intensity of activity. Although the relevant data are limited, it appears that physical activity has similar effects within different populations. An effect of physical activity on breast cancer risk is biologically plausible, since physical activity has direct effects on prevention of weight gain and on postmenopausal obesity, both established breast cancer risk factors. Physical activity has an independent effect on breast cancer risk, aside from those of weight and weight gain, as shown in these studies.

Neither occupational nor non-occupational activity is consistently clearly associated with breast cancer risk reduction. This lack of a clear pattern may be attributable to differences in the physical activity assessment methods and definitions used across studies. Seven of 11 studies of breast cancer that measured occupational activity found risk decreases among the most physically active, while for non-occupational activity, the most physically active

subjects had decreased breast cancer risk in 15 of 22 studies. All five of the studies that measured total activity showed risk decreases (Fraser & Shavlik, 1997; Thune *et al.* 1997; Sesso *et al.*, 1998; Verloop *et al.*, 2000; Friedenreich *et al.*, 2001a). Hence, it appears that total physical activity may be the most etiologically relevant parameter.

The most important time period(s) in life for breast cancer etiology are also unknown. Activity that is sustained throughout lifetime, or at a minimum performed after menopause, may be particularly beneficial in reducing breast cancer risk. Some studies have attempted to measure activity throughout lifetime (Bernstein *et al.*, 1994; Carpenter *et al.*, 1999; Verloop *et al.*, 2000; Friedenreich *et al.*, 2001b) or at specific age periods (Mittendorf *et al.*, 1995; D'Avanzo *et al.*, 1996b; McTiernan *et al.*, 1996; Chen *et al.*, 1997; Gammon *et al.* 1998; Levi *et al.*, 1999b). In these studies, the strongest risk reductions were observed for activity that was sustained throughout lifetime (Verloop *et al.*, 2000; Friedenreich *et al.*, 2001b); however, substantial risk decreases were also observed in studies of activity performed earlier in life (e.g., < 40 years (Bernstein *et al.*, 1994)).

The frequency, intensity, duration of activity that are most associated with risk decreases have also not been systematically examined in all studies. There is inconclusive evidence for a dose–response relationship between increasing intensity of activity and decreasing risk of breast cancer. Indeed, some investigations that measured intensity of activity found the greatest risk decreases for moderate-intensity activity rather than vigorous-intensity activity. Several possible explanations include the low prevalence of high-intensity activity among general female study populations and misclassification of intensity levels. There is more evidence for a trend of decreasing risk with increasing frequency and duration of physical activity.

The 'dose' of physical activity required for breast cancer risk reduction can be estimated from those studies that provided sufficient detail on the activity performed at which risk decreases were observed (Bernstein *et al.*, 1994; Mittendorf *et al.*, 1995; McTiernan *et al.*, 1996; Thune *et al.*, 1997; Carpenter *et al.*, 1999; Rockhill *et al.*, 1999; Moradi *et al.*, 2000a; Verloop *et al.*, 2000; Friedenreich *et al.*, 2001a, b, c). A total of 30–60 minutes of moderate- to vigorous-intensity activity is needed for breast cancer risk reduction. In countries where women achieve higher intensities of activity through occupational and household activities, these activities will be sufficient for breast cancer risk reduction. In countries where women perform sedentary or light occupational and household activities, moderate and vigorous recreational activities are likely to be needed to attain the levels of activity needed for breast cancer risk reduction.

Some of the inconsistencies observed across these studies may be attributable to limitations in the methods used for assessment of physical activity, as the assessment methods used may not have captured the most appropriate parameters of activity in the etiologically relevant periods of life.

Endometrial cancer

Cohort studies

Cohort studies on the relationship of physical activity and endometrial cancer that have included at least 50 cases are presented in Table 41. A prospective study conducted in Sweden found a decreased risk in women who reported "light exercise", "regular exercise" or "hard physical training" compared with those who reported no physical activity during leisure (Terry *et al.*, 1999). Occupational physical activity, as assessed from the job title, was also inversely associated with endometrial cancer risk in another large cohort study in Swedish women (Moradi *et al.*, 1998).

Case–control studies

Seven case–control studies conducted in the USA, Europe and Japan (Table 41) examined the association of physical activity and endometrial cancer (Levi *et al.*, 1993; Shu *et al.*, 1993; Sturgeon *et al.*, 1993; Hirose *et al.*, 1996; Goodman *et al.*, 1997; Olson *et al.*, 1997; Moradi *et al.*, 2000b). All found an inverse association with either occupational or recreational physical activity. The most informative was a large case–control study which included all 709 women aged 50–74 years who were diagnosed with endometrial cancer in Sweden in 1994–95 and 3368 population controls (Moradi *et al.*, 2000b). Information on leisure-time physical activity during childhood, at age 18–30 years and before diagnosis was obtained through mailed questionnaire. Occupational physical activity was estimated from job titles obtained from census information in various calendar years. Risk estimates were adjusted for potential confounders. Women in the highest leisure-time activity category at age 18–30 years were at slightly decreased risk of endometrial cancer (OR = 0.8). A similar decreased risk was found for women in the highest category for recent leisure activity. Inverse associations were also found for occupational physical activity. These associations appeared to be independent of BMI.

Discussion

The results of the limited number of cohort and case–control studies on physical activity and endometrial cancer are consistent in suggesting a 20–40% decrease in risk for the highest levels of physical activity. Most of these studies have taken into consideration other known risk factors for this disease, including body mass, making it unlikely that the observed association was due to confounding. Two studies that reported age-specific results did not suggest any difference in the association by age (Shu *et al.*, 1993; Moradi *et al.*, 1998).

Table 41. Studies on physical activity and risk of endometrial cancer

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Cohort studies							
Zheng *et al.* (1993b), China	1980–84	452	Current occupational activity (3)	SIR = 80	NE	Age	Based on occupational data on census
Moradi *et al.* (1998), Sweden	1967–98	213 708 729 299	Occupational activity at different ages (4)	< 50 yrs: 1.4 (0.67–2.7) 50–59 yrs: 0.62 (0.42–0.91) 60–69 yrs: 0.62 (0.43–0.91) 70+ yrs: 1.6 (0.80–3.1)	No Yes Yes No	Age, residence, socioeconomic status, period of follow-up	Based on national census
Terry *et al.* (1999), USA	1967–92	112	Recreational activity (4)	0.1 (0.04–0.6)	Yes	Age, weight, parity	Swedish twin registry
Case–control studies							
Levi *et al.* (1993), Italy and Switzerland	1988–91	274	Occupational Recreational Household activity (4)	0.7 (0.5–1.0) 0.5 (0.3–1.1) 0.2 (0.1–0.4)	Yes	BMI, age, education, reproductive factors, oral contraceptive and estrogen replacement therapy use, energy intake, study centre	Hospital-based
Shu *et al.* (1993), China	1988–90	268	Occupational: (4) All ≤ 55 yrs	 1.1 (0.63–1.7) 0.62 (0.26–1.4)	 No No	Age, parity, BMI, energy intake	Population-based
Sturgeon *et al.* (1993), USA	1987–90	405	Recent recreational and non-recreational activity (3)	0.83 (0.50–1.4) 0.50 (0.32–0.77)	NE NE	Age, BMI, parity, oral contraceptive and hormone replacement therapy use, smoking, education, study area, recreational or non-recreational activity	Population-based
Hirose *et al.* (1996), Japan	1988–93	145	Recreational activity (3)	0.6 (0.4–0.9)	Yes	Age, first visit year	Hospital-based
Goodman *et al.* (1997), USA	1985–93	332	Recreational Non-recreational (4)	0.9 0.7	No No	Age, parity, oral contraceptive and hormone replacement therapy use, diabetes, BMI, total energy	Population-based

Table 41 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Olson *et al.* (1997), USA	1986–91	232	Vigorous exercise Occupational (3)	0.67 (0.42–1.1) 1.2 (0.76–1.9)	No	Age, reproductive factors, BMI, estrogen replacement therapy use, diabetes, smoking education	Population-based
Moradi *et al.* (2000b), Sweden	1994–95	709	Recreational Occupational at different ages (4)	Recent years: 0.8 (0.6–1.0) 0.8 (0.5–1.1)	 Yes Yes	Age, parity, reproductive factors, BMI, oral contraceptive use, hormone replacement therapy use, smoking	Population-based

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories

Ovarian cancer

Cohort studies

A small number of studies have assessed the association of physical activity with ovarian cancer (Table 42). A Finnish retrospective cohort study comparing cancer risk found an elevated ovarian cancer risk among physical education and language teachers compared with the general population, with no difference between the two groups (Pukkala *et al.*, 1993). A cohort study in Shanghai found that women with occupations entailing high physical activity had the same ovarian cancer risk as women in low-activity occupations (Zheng *et al.*, 1993b). In an analysis of the Iowa Women's Health Study based on 97 cases and seven years of follow-up, Mink *et al.* (1996) found a two-fold increase in risk of ovarian cancer among the most active compared with the least active. In this study, women were asked how often they participated in moderate and vigorous leisure activity. Those who participated in vigorous physical activity two or more times per week and those who participated in moderate activity more than four times per week were considered to have a high physical activity level, regardless of the duration of the activity.

Case–control studies

In a detailed study of physical activity and ovarian cancer, Cottreau *et al.* (2000) interviewed 767 women with ovarian cancer and 1367 population controls about the frequency and duration of their leisure-time activities during each decade of life since adolescence. They found an odds ratio for ovarian cancer of 0.73 (95% CI 0.56–0.94) for women with the highest lifetime level of activity compared with those having the lowest level of activity. When the association was examined by decade of life, the corresponding odds ratios ranged from 0.64 to 0.78. In a hospital-based case–control study in Italy, Tavani *et al.* (2001) studied 1031 cases and 2411 controls, who characterized their physical activity at work as "very heavy", "heavy", "average', "standing" or "mainly sitting". Physical activity during leisure time was assessed based on the number of hours per week spent in sports or household activities. After adjustment for other risk factors for ovarian cancer, the odds ratio for the highest versus lowest levels of occupational activity at age 50–59 years was 0.76 (95% CI 0.48–1.2). The corresponding OR for age 30–39 years was 0.67 (95% CI 0.47–0.98). No association was found with leisure-time activity.

Discussion

Only five studies have reported on physical activity and ovarian cancer and their findings have been inconsistent. The larger and more recent studies have included information on potential confounders. However, no firm conclusion on a possible association between physical activity and ovarian cancer can be drawn.

Prostate cancer

The great majority of the studies of the association between prostate cancer and physical activity have been conducted in developed countries, where participation in prostate cancer screening may differ between men who exercise and those with a more sedentary lifestyle. Thus, of particular interest are studies that focused on more advanced prostate tumours, the diagnosis of which is less dependent on participation in screening.

Cohort studies

Table 43 summarizes the prospective studies on physical activity and prostate cancer with at least 100 cases. Out of eight reports from cohort studies, six reported no association (Severson *et al.*, 1989; Lee *et al.*, 1992; Thune & Lund, 1994; Hartman *et al.*, 1998; Giovannucci *et al.*, 1998; Liu *et al.*, 2000) and two observed a mostly weak protective effect (Clarke & Whittemore, 2000; Lund Nilsen *et al.*, 2000). Some of the null studies observed an inverse association in subgroup analyses (e.g., Thune & Lund, 1994; Hartman *et al.*, 1998; Giovannucci *et al.*,1998), as described below.

Lee *et al.* (1992) found that Harvard alumni aged 70 years or older who expended more than 4000 kcal [16 800 kJ] per week in college or ten years later were at 50% decreased risk (95% CI 0.3–1.0) of developing prostate cancer, compared with those who expended less than 1000 kcal [4200 kJ] per week at either assessment. No association was found in younger subjects. Severson *et al.* (1989) reported no association between usual physical activity and prostate cancer in a cohort study of Japanese men in Hawaii. Similarly, in the Physicians' Health Study, a randomized trial of low-dose aspirin and β-carotene among 22 071 US men, physical activity (assessed as the frequency of exercise vigorous enough to work up a sweat) was unrelated to risk of prostate cancer (Liu *et al.*, 2000). In the other cohort studies, physical activity was inversely associated with prostate cancer, overall or in subgroup analyses. One of these (Clarke & Whittemore, 2000) used the data from the NHANES I Epidemiological Follow-up Study. Participants were asked to rate their physical activity during a normal day and during their leisure activities as high, moderate or low. The most recent and detailed analysis of this cohort, based on 201 cases, showed that men who reported high levels of non-recreational physical activity had decreased prostate cancer risk compared with very sedentary men. This association was stronger for African Americans (RR = 0.27; 95% CI 0.12–0.60) than for Caucasians (RR = 0.60; 95% CI 0.44–1.3). Moderate levels of recreational activity were weakly associated with increased prostate cancer risk among African Americans but not among Caucasians, suggesting that only high physical activity levels were protective. A Norwegian study found that men who walked in their job and engaged in regular physical training

Table 42. Studies on physical activity and risk of ovarian cancer

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Cohort studies							
Pukkala *et al.* (1993), Finland	1958–92	51	Current occupational title	SIR (vs general population) for: Physical activity teachers: 1.7 (0.8–3.2) Language teachers 1.6 (1.1–2.1)	NE	Age	Based on national incidence figures
Zheng *et al.* (1993b), China	1980–84	595	Current occupational activity (3)	SIR = 1.02	NE	Age	Based on occupa-pational data on census
Mink *et al.*, (1996), USA	1985–92	97	Recreational activity:				
			Moderate (4)	1.6 (0.87–2.9)	Yes	Age	Post-menopausal women
			Vigorous (4)	2.5 (1.0–6.3)	Yes	Age	
			Overall index (3)	2.1 (1.2–3.5)	Yes	Age, smoking, education, parity, family history, waist/hip ratio	
Case–control studies							
Cottreau *et al.* (2000), USA	1994–98	767	Recreational index at different ages (3)	Lifetime 0.73 (0.56–0.94)	Yes	Ae, parity, estrogen use, family history, BMI, education, race, tubal ligation	Population-based
Tavani *et al.* (2001), Italy	1992–99	1031	Occupational	30–39 years:	Yes	Age, education, study centre, BMI, reproductive factors, family history, energy intake, estrogen use	Hospital-based
			Recreational at different ages (3)	0.67 (0.47–0.98) 0.86 (0.65–1.1)	No		

* Either a significant test for trend or significant relative risks for intermediate exposure categories

Table 43. Studies of physical activity and risk of prostate cancer

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Cohort studies							
Severson *et al.* (1989), USA	1965–66	206	24 h index of all activities plus time sleeping (3)	1.0 (0.75–1.5)	No	Age, BMI	Hawaii Japanese
Lee *et al.* (1992) USA	1962–88	419	Recreational activity (3)	0.88 (0.64–1.2)	No	Age	College alumni
Thune & Lund (1994), Norway	1972–91	220	Occupational (4) Recreational (3)	0.81 (0.50–1.3) 0.87 (0.57–1.3)	NE NE	Age, region, BMI	Different counties in Norway
Giovannucci *et al.* (1998), USA	1986–94	200	Total Vigorous recreational activity (4)	0.72 (0.44–1.2) 0.46 (0.24–0.89)	No No	Age, height, vasectomy, diabetes smoking, diet	Metastatic tumours
Hartman *et al.* (1998), Finland	1985–94	317	Occupational (4) Leisure (2)	1.2 (0.74–2.0) 0.9 (0.73–1.1)	NE NE	Age, urban, smoking, history of benign prostate hypertrophy, intervention	ATBC trial
Clarke & Whittemore (2000), USA	1971–92	201	Non-recreational (3) or recreational (3) activity	0.58 (0.37–0.89) 0.85 (0.58–1.3)	Yes No	Age, education, family history	NHANES I
Liu *et al.* (2000) USA	1982–95	982	Vigorous exercise (4)	1.1 (0.91–1.4)	No	Age, height, intervention, smoking, alcohol, diabetes, plasma cholesterol, vitamins, hypertension, BMI	Physicians' Health Study
Lund Nilsen *et al.* (2000), Norway	1984–95	644	Recreactional (3) or occupational (2) activity	0.80 (0.62–1.0) 1.0 (0.82–1.3)	No NE	Age	Health screenees
Case–control studies							
Brownson *et al.* (1991), USA	1984–89	2878	Occupational activity (3)	0.7 (0.6–0.8)	Yes	Age, smoking	Cancer registry data
Le Marchand *et al.* (1991b), USA	1977–83	214	Lifetime occupational activity (4)	2.0 (1.1–3.3)	Yes	Age, ethnicity, income, education	Population-based Age > 70 years
West *et al.* (1991) USA	1984–85	358	Total energy expended (2)	Aggressive tumours 2.0 (0.8–5.2)	NE	Age	Population-based controls

Table 43 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Hsing *et al.* (1994), China	1980–84	264	Occupational activity (3)	SIR = 0.92 (0.7–1.1)	No	Age	Population-based
Andersson *et al.* (1995), Sweden	1989–92	256	Adolescent physical activity (3)	0.7 (0.4–1.1)	No	Age, urban, farming	Population-based
Whittemore *et al.* (1995), USA, Canada	1987–91	1655	Time in light or vigorous activity	Means: no association	No	Age, ethnicity, region	Population-based
Ilic *et al.* (1996), Yugoslavia	1990–94	101	Occupational activity (2)	3.9 (2.1–7.2)	NE	Age, occupational exposure, nephrolithiasis no. of brothers, no. of sexual partners	Hospital-based
Sung *et al.* (1999), Taiwan	1995–96	90	Recreational exercise	2.2 (1.2–4.0)	NE	Age, education, BMI, diet	Hospital-based
Villeneuve *et al.* (1999), Canada	1994–97	1133	Leisure (strenuous) activity (5)	0.7 (0.4–1.4)	No	Age, province, race, smoking, BMI, diet, income, family history	Population-based

* Either a significant test for trend or significant relative risks for intermediate exposure categories

during leisure time had significantly lower risk of prostate cancer (RR = 0.45; 95% CI 0.20–1.0) compared with sedentary men (Thune & Lund, 1994). In the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study, a chemoprevention trial among smokers in Finland, no association between occupational activity and prostate cancer was found (Hartman *et al.*, 1998). However, among working men, there was an inverse association with leisure-time physical activity. Participants who ranked their exercise level as "heavy" had a relative risk of 0.7 (95% CI 0.5–0.9) compared with those who described themselves as sedentary during leisure. Giovannucci *et al.* (1998) analysed the data from the Health Professionals Follow-up Study, the largest and most informative study of lifestyle and prostate cancer published to date. Subjects reported in a self-administered questionnaire the average time spent on a variety of non-occupational activities. No relationship was found with total or advanced prostate cancer for total, vigorous or non-vigorous physical activity. For metastatic prostate cancer, no linear trend was found for these activities, but a significantly lower risk was observed in the highest category of vigorous physical activity (RR = 0.46; 95% CI 0.24–0.89). Finally, in a large cohort study in Norway in which men self-characterized their leisure-time and occupational physical activity as low, medium or high, a weak inverse association was found with recreational exercise, whereas occupational physical activity was unrelated to risk (Lund Nilsen *et al.*, 2000).

Case–control studies

Case–control studies that included at least 100 cases are summarized in Table 43; the results have been inconsistent. Among the five studies reporting on occupational physical activity, two observed an increased risk with high activity (Le Marchand *et al.*, 1991b; Ilic *et al.*, 1996), one showed no association (Hsing *et al.*, 1994) and two reported decreased risks (Brownson *et al.*, 1991; Villeneuve *et al.*, 1999). Among the case–control studies that reported on usual or leisure-time physical activity, two found no association (West *et al.*, 1991; Whittemore *et al.*, 1995) and one found an increased risk (Sung *et al.*, 1999). In a case–control study in Utah, USA, West *et al.* (1991) found that men aged 45–67 years who were in the highest quartile of total energy expenditure were at slightly increased risk of 'aggressive' prostate tumours (a group including localized undifferentiated and advanced tumours). No association was found for older men. Two case–control studies reported on physical activity at an early age in relation to prostate cancer risk. In a subset of their Canadian subjects, Villeneuve *et al.* (1999) inquired about participation in strenuous and moderate leisure-time activity and assessed occupational physical activity at different periods of life (mid-teens or early 20s, early 30s, early 40s and two years before diagnosis). They found no association with prostate cancer, except for a protective effect of strenuous occupational physical activity performed in the mid-teens or early 20s (OR = 0.6; 95% CI 0.4–0.9 for strenuous activities compared with sitting activities). In a population-based case–control study in Sweden, Andersson *et al.* (1995) found that subjects who reported being more physically active than their classmates around the time of puberty were at somewhat lower risk of prostate cancer (OR = 0.7; 95% CI 0.4–1.1) compared with those who said that they exercised less than their classmates. Thus, the data are inconsistent with regard to the period of life at which physical activity may be most relevant.

Discussion

Less than twenty epidemiological studies were available to assess the relationship of physical activity to prostate cancer. As for other cancer sites, these studies are difficult to evaluate due to the differences in the methods used to assess physical activity. Questionnaires have focused either on usual physical activity (i.e., amount of time spent at various levels of physical activity during a usual day) or on leisure-time activities and the questions have ranged from those covering details of the frequency and duration of various activities to simple questions asking the subjects to rate themselves as sedentary, moderately active or very active. Studies of occupational exercise have typically assumed that a man in a particular job has performed the level of physical activity that has been estimated as the average level for his job category and this for the duration of his employment in this job. However, despite these methodological differences, a majority of studies have suggested a protective effect; the relationships have tended to be of moderate strength and sometimes were observed only in subgroups. The findings in well conducted cohort studies of an inverse association with metastatic disease and in groups of low socioeconomic status (e.g., African Americans) suggest that the observed effects may not be due to detection bias.

Overall, the available evidence suggests that physical activity may protect against prostate cancer.

Kidney cancer

Cohort studies

In a Swedish study, occupational physical activity was inversely associated with renal-cell cancer risk among men but not in women (Lindblad *et al.*, 1994). No association was found in the Harvard Health Alumni study (Paffenbarger *et al.*, 1987).

Case–control studies

One case–control study reported a protective effect of occupational activity on renal-cell cancer risk among men (Bergström *et al.*, 1999). Three others, however, found no association with physical activity (Goodman *et al.*, 1986;

Mellemgaard *et al.*, 1994, 1995). One of these studies was a multi-centre population-based case–control study conducted in Australia, Denmark, Germany, Sweden and the USA that included 1732 cases (Mellemgaard *et al.*, 1995).

Discussion

The results from the few published studies regarding the association between physical activity and renal-cell cancer are inconsistent for both occupational and recreational physical activity and do not permit an adequate assessment to be made.

Lung cancer

Five cohort studies (Paffenbarger *et al.*, 1987; Severson *et al.*, 1989; Steenland *et al.*, 1995; Thune & Lund, 1997; Lee *et al.*, 1999a) and two case–control studies (Brownson *et al.*, 1991; Dosemeci *et al.*, 1993) on physical activity and lung cancer have been reported (Table 44). Earlier publications from the NHANES I study (Albanes *et al.* 1989) and the Harvard Health Alumni study (Lee & Paffenbarger, 1994) were excluded because the subsequent follow-ups from the same cohorts updated the results.

Cohort studies

A lower risk of lung cancer was associated with physical activity in all of the cohort studies. The largest studies were the Harvard Health Alumni Study (Lee *et al.*, 1999a) and a population-based cohort in Norway (Thune & Lund, 1997). The Norwegian cohort study measured both recreational and occupational activity and found a 30% decreased risk when these activities were combined into a total activity variable for the male study subjects (Thune & Lund, 1997), but no comparable risk decrease was observed for females. In the Harvard Health Alumni study (Lee *et al.*, 1999a), even stronger risk decreases were associated with total energy expended, with 40% decreases observed among men who expended the greatest amount of energy. Overall, the risk decreases in these studies ranged from 20–60% for both non-occupational and occupational physical activity, with an inverse dose–response relationship.

Case–control studies

The two case–control studies of occupational physical activity do not support a decrease in risk of lung cancer; one observed an increased risk (Brownson *et al.*, 1991) and the other found no effect (Dosemeci *et al.*, 1993). Given the fact that these two studies were both hospital-based case–control studies and used only occupational title to assess physical activity, it is difficult to draw firm conclusions from these results.

Discussion

Five of the seven studies reviewed demonstrated a decreased risk of lung cancer among the most physically active subjects. The risk decreases ranged from 20 to 60% and evidence for a dose–response relationship was observed. This effect could be confounded by smoking which, although it was appropriately controlled for in these studies, could have been associated with other lung diseases (e.g., chronic obstructive lung disease) among the study participants. Given the uncertainty of the association and the limited amount of data available, the evidence for an association remains inconclusive.

The level of activity that appears to confer a protective effect on lung cancer can be estimated from the two largest studies. These studies indicate that four hours per week of hard leisure-time activity (Thune & Lund, 1997) and participation in activities of at least moderate activity (> 4.5 MET), but not light activity (< 4.5 MET) (Lee *et al.*, 1999), reduced lung cancer risk independently after adjustment for smoking and other possible risk factors. Different effects of physical activity on various histological types of lung cancer have also been reported (Thune & Lund, 1997). Physical activity may reduce the concentration of carcinogenic agents in the airways, the duration of agent–airway interaction and the amount of particle deposition through increased ventilation and perfusion.

Testicular cancer

Two cohort studies (Paffenbarger *et al.*, 1992; Thune & Lund, 1994) and five case–control studies (Brownson *et al.*, 1991; Dosemeci *et al.*, 1993; UK Testicular Cancer Study Group, 1994b; Gallagher *et al.*, 1995; Srivastava & Kreiger, 2000) have been conducted on the association between physical activity and testicular cancer (Table 45). The two cohort studies both had sample sizes of less than 100 cases and have been excluded from the table but are mentioned briefly below.

Cohort studies

No effect of physical activity on testicular cancer risk was found in either of the two cohort studies (Paffenbarger *et al.*, 1992; Thune & Lund, 1994).

Case–control studies

A large case–control study conducted in the United Kingdom found a decreased risk of testicular cancer for recreational activity performed either early in life or during the reference year (UK Testicular Cancer Study Group, 1994b). These results were corroborated by a subsequent population-based case–control study conducted in Canada that found risk decreases for recreational activity performed at age 21 years and five years before diagnosis (Gallagher *et al.*, 1995). The results from these two studies and two earlier case–control studies that found either no effect (Dosemeci *et al.*, 1993) or a decreased risk with occupational activity (Brownson *et al.*, 1991) are in contrast to those of the most recent study, that observed an increased risk among physically active men (Srivastava & Kreiger, 2000). In this

Table 44. Studies of physical activity and risk of lung cancer

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Cohort studies							
Paffenbarger *et al.* (1987), USA	1951–72	M+F: 112	Occupational titles (4)	0.4	NE	Age	Mortality study
Severson *et al.* (1989), USA	1965–86	M: 192	24-hour physical activity index as sum of time in all activities plus sleeping (3)	0.7 (0.5–1.0)	Yes	Age, BMI, smoking	Hawaii Japanese
Steenland *et al.* (1995), USA	1971–87	M: 151 F: 59	Current non-recreational activity (3)	M: 0.8 (0.5–1.4) F: 0.7 (0.3–1.7)	NE	Age, BMI, smoking, alcohol, income, recreational activity	NHANES 1 study Longer follow-up of cohort reported in Albanes *et al.* (1989)
Thune & Lund (1997), Norway	1972–91	M: 413 F: 51	Recreational and occupational activity (2, 3 or 4)	Occupational activity M: 1.0 (0.7–1.4) F: 0.8 (0.3–2.1) Recreational activity: M: 0.7 (0.5–1.0) F: 1.0 (0.4–2.8) Total activity: M: 0.7 (0.5–1.0) F: 0.9 (0.2–3.6)	No (M+F) Yes No NE	Age, geographical area, smoking habits, BMI	Age 20–49 years
Lee *et al.* (1999a), USA	1962–88	M: 245	Current walking, stair climbing and recreational activity at baseline (4)	Energy expended: 0.6 (0.4–0.9) Distance walked 0.7 (0.5–0.9) Stairs climbed: 0.7 (0.5–1.0) Moderate recreational activities: 1.0 (0.7–1.5) Vigorous recreational activities: 0.6 (0.4–1.0)	Yes Yes No No Yes	Age, smoking habits, BMI and other three components of physical activity	College alumni Update of Lee & Paffenbarger (1994)

Table 44 (contd)

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Case–control studies							
Brownson *et al.* (1991), USA	1984–89	M: 4700	Occupational titles (3)	1.3 (1.1–1.7)	Yes	Age, smoking	Cancer registry data
Dosemeci *et al.* (1993), Turkey	1979–84	M: 1148	Occupational titles to estimate energy expenditure over lifetime (3)	1.0 (0.8–1.3)	No	Age, smoking, socioeconomic status	Hospital-based

RR, relative risk; OR, odds ratio; SIR, standardized incidence ratio; BMI, body mass index.

* Either a significant test for trend or significant intermediate relative risks for intermediate exposure categories

Table 45. Studies of physical activity and risk of testicular cancer

Author, date, study location	Study dates	No. of cases	Activity definition (no. of categories)	Relative risk (highest vs lowest categories) (95% CI)	Trend*	Adjustment for confounding	Comments
Case–control studies							
Brownson *et al.* (1991), USA	1984–89	252	Occupational titles (3)	0.5 (0.3–0.8)	Yes	Age, smoking	Cancer registry data
Dosemeci *et al.* (1993), Turkey	1979–84	191	Occupational titles to estimate energy expenditure over lifetime (3)	1.0 (0.5–1.8)	No	Age, smoking, socioeconomic status	Hospital-based
UK Testicular Cancer Study Group, (1994b), UK	1984–87	793	Recreational activity at age 20 and at reference age (6)	Age 20: 0.6 (0.4–0.9) Reference age: 0.5 (0.3–0.9)	Yes	Age, undescended testis, inguinal hernia before age 15 y	Population-based
Gallagher *et al.* (1995), Canada	1980–85	510	Lifetime occupational and recreational activity (4)	Recreational activity: 0.7 (0.5–0.9) Occupational activity: 0.9 (0.6–1.3)	Yes No	Age, ethnic origin, undescended testis, inguinal hernia	Population-based
Srivastava & Kreiger (2000), Canada	1995–96	212	Frequency of moderate recreational activity at different ages (4 or 5) Intensity of occupational activity by life period (4)	Recreational Teens: 2.4 (1.2–4.6) Early 30s: 1.7 (0.7–4.4) 2 yrs before: 1.4 (0.6–3.3) Cumulative lifetime: 1.0 (0.4–1.7) Occupational Early 20s: 1.7 (0.9–3.0) Early 30s: 1.3 (0.6–2.8) 2 yrs before: 0.9 (0.5–1.9) Cumulative lifetime: 0.8 (0.3–1.7)	NE	Age, BMI, education, smoking, marital status	Population-based

RR, relative risk; OR, odds ratio; SIR, standardized incidence ratio; BMI, body mass index
* Either a significant test for trend or significant relative risks for intermediate exposure categories

Canadian study, a 2.4-fold increase in risk was observed among subjects who participated in strenuous leisure-time activity more than five times per week during adolescence as compared with those who performed strenuous leisure-time activity less than once a month. At later ages and for cumulative lifetime exposure, the risks associated with recreational activity for the highest versus lowest quartiles were not elevated nor statistically significant. Likewise, increased risks were not statistically significant for occupational activity. Hence, it appears that in this study, only activity performed during adolescence was associated with increased testicular cancer risk.

Discussion

Three of the seven studies have found decreased testicular cancer risks among the most physically active participants. The risk decreases were fairly modest and since one study noted an increased risk and three a null effect, the results remain inconsistent and weak regarding this putative association. Little evidence exists for a dose–response relationship. The studies also suffered from weak exposure data and limited control for confounding. Overall, there is insufficient evidence to draw any conclusion on the nature of the relationship between physical activity and testicular cancer.

Population attributable risk

In summary, there is considerable evidence that physical inactivity is associated with some of the most common cancers. The proportion of any disease due to a risk factor in a population is determined by both the size of relative risk and the prevalence of the risk factor in the population. That proportion, often referred to as the population attributable risk (PAR), has not been estimated for most of the cancer sites reviewed here. Slattery *et al.* (1997a) estimated, from the results of a large US study, that the PAR for physical inactivity (20–25% of the population reported no activity) was 13% for colon cancer. This is similar to the PAR of 14% for colon cancer estimated by La Vecchia *et al.* (1999b) in an Italian study. Mezzetti *et al.* (1998) estimated that 11% of breast cancer might be attributable to physical inactivity. Although the measures of physical activity vary widely between the studies reviewed here, it is likely that in many industrialized countries the PARs for colon and breast cancers are at least this large. Random measurement error will result in underestimation of the size of relative risks. These PAR values for physical inactivity may therefore be substantially underestimated, perhaps by a factor of two. It is also important to point out that physical activity and weight control are clearly interrelated, as physical activity is an important factor in lifetime weight maintenance. Therefore, all the attributable risks for elevated BMI for colon, breast and endometrial cancers could also be interpreted as risks that are attributable, in part, to physical inactivity.

Intervention studies of intermediate markers of cancer

Studies of effects on cancer incidence or mortality of interventions to lose weight or to increase physical activity would require very large numbers (usually tens of thousands) of participants followed up for long periods of time. Such endeavours entail considerable difficulties in recruiting and retaining participants and in funding. Small randomized clinical trials of effects of exercise on biomarkers for cancer can provide insights into the biological effects of weight loss or physical activity interventions. In this section, the term 'intervention study' refers to a study in which a behavioural, medical or other intervention is prescribed to a group of study participants. 'Randomized controlled clinical trial' refers to a study in which participants are recruited, screened for eligibility and interest, randomly assigned to one or more interventions or to one or more control groups, and followed forward in time for the development of end-points. These end-points can be disease-specific morbidity and mortality or can be biomarkers of disease or health.

Clinical trials can focus on one or two specific interventions, so that the effect of a given level of exercise for a defined period of time can be assessed. The specific physiological aspects of physical activity can be studied. Many of the difficulties associated with measuring exercise exposure in observational studies can be avoided, because direct observation of study participants exercising can be made and physiological measures of fitness can be used. Properly designed and executed randomization can minimize bias from potential confounding variables. Homogeneity of exercise exposure can be avoided, because the trial design can include one or more groups with defined exercise prescriptions and, usually, a control condition. Measuring change in exercise exposure is difficult in observational settings because most people do not significantly change their exercise habits, and because recall of changes in physical activity can be difficult. Clinical trials can be designed so that change in physical activity is prescribed and maximized to allow assessment of effect. Randomized trials can focus on specific populations such as high-risk individuals, who may be highly motivated to make changes in exercise behaviour. The clinical trial design allows assessment of effects of physical activity on intermediate end-points and biomarkers, which is difficult to do in observational studies. Synergistic or antagonistic effects with other behaviours or with treatments can be studied in clinical trials, especially with factorial designs with two or more interventions. Finally, several end-points can be efficiently measured in a single trial. There are some limitations in randomized clinical trials. Volunteers for such studies

are a selected group and may not represent the general population of overweight, obese or sedentary persons. The range of exercise or dietary exposure is normally limited to the type of intervention and individual adherence.

There have been a small number of intervention studies of weight loss or physical activity effect on intermediate markers of cancer. In addition, intervention studies without randomization or without a control group have been reported. Because of the potential for biased results in uncontrolled intervention studies, the optimal design for intervention studies is the randomized controlled trial. In several instances, trials have been conducted to assess intermediate markers of coronary or other diseases. The results of these studies are applicable to cancer in so far as the intermediate markers and biomarkers are shared.

Weight reduction

Hormones

Observational data suggest links between diet, overweight and risk of certain cancers, as well as between certain metabolic hormones and cancers. A full discussion of how diet and weight loss might affect sex and metabolic hormones and the proteins to which they bind in blood is included in Chapter 4. There have been many intervention studies, but few well powered randomized controlled trials, assessing the effect of weight loss on endogenous hormones. The studies in subjects with normal weight were not planned as such; weight loss occurred rather as a secondary effect of a change in dietary intake (of, for example, lowered fat, increased fibre or increased vegetables and fruits). Overall, there is clear evidence of reduction in circulating insulin levels with either type of weight loss. Consistent evidence from controlled and uncontrolled clinical trials shows that weight loss leads to increased levels of SHBG. There is no convincing evidence from intervention studies that weight loss can reduce circulating estrogen levels in premenopausal women. However, some types of dietary change, such as increased fibre and decreased fat, may cause decreases in estrogen levels. A smaller body of data suggests that weight loss can affect IGF and IGFBP levels. Hormonal effects vary with the length of intervention and follow-up.

Mammographic densities

There is considerable evidence that women with extensive areas of mammographic densities are 4–6 times more likely to develop breast cancer than those with little or no density on their mammogram. High-risk mammographic patterns may be used as a surrogate end-point for breast cancer in etiological research as well as in prevention studies. In a randomized dietary intervention study, Boyd *et al.* (1997) examined the effect of a two-year low-fat, high-carbohydrate diet on breast radiological densities. Women with radiological densities (n = 817) in more than 50% of the breast area on mammography were recruited and randomly allocated to an intervention group taught to reduce their dietary intake of fat (mean, 21% of energy) and increase their complex carbohydrate intake (mean, 61% of energy) or to a control group (mean, 32% from fat and 50% from carbohydrates). Mean body weight was similar at baseline (62.3 and 62.7 kg in the intervention and control groups, respectively, $p = 0.47$), decreased 0.3 kg in the intervention group, and increased 0.9 kg in the control group ($p = 0.0003$). After two years, the area of density was reduced by 374 mm^2 (6.1%) in the intervention group compared with an average of 128 mm^2 (2.1%) in the control group (p = 0.01). The effect of the intervention on breast densities, however, was only marginally significant after weight change and change in menopausal status were taken into account, suggesting that part of the dietary effect may have been mediated by weight loss.

Colorectal polyps

The Polyp Prevention Trial has provided data on effects of diet on colorectal polyp recurrence (Schatzkin *et al.*, 2000) This trial was conducted in 2079 men and women aged 35 years or older who had one or more incident colorectal adenomatous polyps removed. Participants were randomized to either a low-fat (20% of energy), high-fibre (18 g/1000 kcal [4.3 g/1000 kJ]), and high fruits and vegetables (3.5 servings per 1000 kcal [0.8 servings per 1000 kJ]). Although the intervention was not focused on weight loss, the intervention participants lost a mean of 1.4 lb [0.64 kg], while controls gained an average of 1.0 lb [0.45 kg] during the course of the study. After four years of follow-up, there was no difference in the rate of polyp recurrence between the groups. The overall weight loss observed in this trial was too small to be informative.

Physical activity

Hormones

As for weight control, exercise causes significant reductions in circulating insulin levels in normal, hyperinsulinaemic and diabetic persons. Observations of amenorrhoea and other menstrual abnormalities in trained female athletes have led to closer scrutiny of the effects of exercise on hormonal patterns in girls and young women. There have been several uncontrolled trials of exercise effect on hormones, as discussed in Chapter 4. Overall, there is moderately strong evidence that vigorous exercise lowers endogenous estrogen levels in premenopausal women. There are no published data from intervention studies in postmenopausal women. In men and women of all ages, exercise

raises SHBG levels. Effects of exercise on IGF levels have been tested in few intervention studies, with variable results.

Immune function

Interest in effects of exercise on immune function stems from observations of impaired immunity in highly trained athletes. While immune status has not been clearly linked to cancer etiology, it is biologically plausible that immune function is important in the development and growth of cancers. Many small uncontrolled trials have assessed effects on immune function of training-level and moderate-intensity exercise, with varying results depending on baseline fitness level, age and the type of immune parameter studied. Overall, moderate-intensity exercise appears to improve immune function, as discussed more fully in Chapter 4.

Summary

There have been many intervention studies of the effects of weight loss and physical activity on insulin, but fewer on sex hormones and immune function. Nevertheless, there are indications that various sex and metabolic hormones, immune function and other biomarkers of cancer are affected by weight loss and exercise.

Experimental systems

Animal experiments are classified as studies of energy restriction, diet restriction or exercise. These categories should be viewed as experimental approaches by which prevention of weight gain in animals is achieved. The majority of studies of restriction or physical activity in experimental animal models of carcinogenesis do not involve weight loss; instead, the animals are in a state of positive energy balance but achieve a smaller mass with a lower percentage of body fat than animals allowed free access to diet or sedentary animals. This situation directly parallels and models conditions in humans associated with different levels of cancer risk. Thus the experimental carcinogenesis studies reviewed below do not involve extreme underweight (starvation), as exemplified by anorexia nervosa, nor do they model obesity.

It is not at present known, and may never be known, to what extent healthy individuals in modern societies restrict their dietary intake. The range of restrictions or physical activity used in animal experiments can be viewed as an approach to preventing adult body weight gain in these animals and is intended to resemble the range of energy balances that occur in healthy people. However, healthy rodents differ from healthy humans in that they experience adult linear growth.

Design issues in diet, exercise and experimental carcinogenesis

Selection of model

Experimental animal models must be selected that mimic as closely as possible the human disease. Characteristics that should be considered in choosing a model include the similarity of tumour morphology and biological traits such as (hormonal) responsiveness to those seen in humans. Such models are available for many organ sites. For example, in rat models for breast cancer, not only are tumours morphologically similar to their human counterparts, but the majority are ovarian steroid-responsive and factors such as full-term pregnancy protect against disease occurrence. *N*-Nitrosobis-2-(oxopropyl)amine (BOP)-induced ductular pancreatic cancer in the Syrian hamster is a model that has been useful in studying aspects of human pancreatic cancer that cannot be addressed with humans (Pour *et al.*, 1993), whereas other induced pancreatic tumours are acinar cell carcinomas, which are not a common pancreatic lesion in humans. Furthermore, it is best to minimize the time of treatment with a chemical carcinogen, unless the chemical carcinogen is one to which humans are chronically exposed. A short-term carcinogen treatment will allow the investigator to feed the experimental diet or provide the physical activity intervention of interest at times when the chemical carcinogen is not being administered. The impact of diet or exercise on the metabolism of a chemical carcinogen to which people are not exposed may be of scientific interest, but the observations may have limited relevance to the prevention of human cancer.

Selection of diet

Both cereal-based and semi-purified diets have been used in studies of dietary impact on carcinogenesis. It is of the utmost importance that the control diet in either case be adequate in all nutrients, not excessive in any component, and that it be free of potentially toxic components. Cereal-based diets have the advantage that they are designed using whole food ingredients. However, the food ingredients are not commonly used in the same manner in human diets and the complexity of their composition makes it difficult to attribute observations to a particular nutrient or constituent. This issue is addressed below for studies of dietary restriction with cereal-based diets. Semi-purified diets have the advantage that each component can be modulated independently of other constituents in a highly controlled fashion, but since these diets do not use common human foods, extrapolation to such foods must be made with caution.

Design of intervention protocol

Dietary or exercise interventions should be provided separately from the chemical carcinogen in studies where the cancer-causing stimulus is not a cancer-causing agent for human disease. With such models, it is common to apply the dietary or activity intervention after exposure to the carcinogenic stimulus, in order to obtain information on the

development of the disease process. In cases where the cancer-causing stimuli do represent conditions that may induce human cancer, it is important to assess the impact of the intervention strategy both on the cancer-induction phase (preceding and at the time of carcinogen treatment) and on the promotion/progression (development) of the cancer (following treatment with the carcinogen). Models involving a short induction phase provide the possibility of assessing the impact of diet on early or late stages of promotion. If tumours are allowed to develop before the intervention, it is possible to assess the impact of the intervention on the regression or progression of the lesions. Finally, recently developed genetically modified animal models of human cancers allow scientists to determine if interventions of interest can prevent the development of cancer that is driven by genes known to be mutated in human cancer. Such studies should provide information on how diet or physical activity may be useful in the prevention of cancer in people with particular genetic predisposition.

Weight control

Weight control involves balancing energy intake with energy expenditure to maintain a targeted body weight and presumably body composition. In general, energy restriction has been shown to be associated with cancer prevention, while an excess intake of energy is associated with an increased risk for cancer. While some evidence implies a role of body fat in these effects, other results suggest that the effects are not due to body fat *per se*. Thus, in assessing the cancer-preventive effects of weight control, predominant attention is given here to the role of energy restriction. In the literature, energy restriction is also referred to as calorie restriction, dietary restriction or food restriction. These terms are not synonyms. Energy restriction is used in this volume to characterize studies in which the energy intake was selectively reduced while all micronutrients were fed at the same level as in the control group. The terms food restriction and diet restriction are used to refer to underfeeding of a complete diet such that less of all nutrients and dietary factors is ingested; this approach can lead to an intake of micronutrients and/or macrocomponents that is incompatible with optimal health. The term dietary restriction is used for such protocols in this review. Dietary restriction, which does not allow the investigator to detect effects due specifically to a limitation in dietary energy, was frequently used in early studies of restriction. With the cereal-based diets used until the 1940s, dietary restriction was the most expedient approach and is still sometimes used. Such studies can provide valuable insights, but their results must be interpreted with caution. The earliest experimental studies of dietary restriction assessed the growth of transplanted tumours. Owing to the limited relevance of transplantable tumour model systems to primary cancer prevention, these studies (see reviews by Tannenbaum & Silverstone, 1953; Birt, 1987; Weindruch *et al.*, 1991; Kritchevsky, 1992, 1999) are not considered in detail below. Examples of studies with dietary restriction are included in this report only if they provide information not available with energy restriction protocols in which energy intake was selectively reduced. Calorie restriction and energy restriction are the terms generally applied to experimental approaches in which diets are formulated so that, when animals are fed different numbers of calories, they still receive the same levels of other nutrients, such that the only variable is energy intake.

The present review of energy restriction and dietary restriction approaches to prevent excessive adult body weight gain as cancer-preventive strategies covers dietary restriction studies only if similar energy restriction studies have yielded comparable results. The aim was to ensure that the body weight maintenance resulting from the dietary restriction was likely to be the cause of the cancer prevention, and the parallel energy restriction protocol would provide this evidence. Dietary restriction protocols without parallel energy restriction studies must be viewed with caution, since a multitude of dietary constituents that may not affect body weight but are known to influence cancer rates are also reduced in these diets.

Studies described below are summarized in Table 46.

Colon

Chemically induced rodent colon tumours can be considered to model those in humans for the following reasons. They are induced more frequently in the distal part of the colon, which is the preferential site of the human lesions. The developmental sequence from preneoplastic lesions, aberrant crypt foci, to adenoma and carcinoma is well established. Furthermore, a similar incidence of K-*ras* mutations has been observed in adenocarcinomas in rats, mice and humans.

Reddy *et al.* (1987) reported the inhibition of azoxymethane (AOM)-induced colon carcinogenesis in rats by continuous energy restriction starting four days after AOM treatment. Colon carcinogenesis in rats was not inhibited when dietary restriction was initiated at day 63 after treatment with methylazoxymethanol (MAM) or when animals were fed *ad libitum* or fasted every other day from day 8 or 31 after MAM treatment (Pollard *et al.*, 1984). Newberne *et al.* (1990) studied the preventive effects of pre- and postnatal energy restriction against colon cancer in rats treated with dimethylhydrazine (DMH). After birth, rat litters were adjusted to four or eight rats per litter. The rats in litters of four and fed *ad libitum* became heaviest and developed the greatest number of tumours. Rats in litters of four, but pair-fed the

Table 46. Studies of prevention of spontaneous and carcinogen-induced tumours by dietary restriction in experimental animals

Organ site, species, strain (sex)	Age at beginning of study (wk)	No. of animals per group	Carcinogen/ dose/route	Dietary restriction/ amount, type	Timing of restriction	Prevention effect	Summarized effect	Reference
Colon								
Rat								
Lobund Sprague-Dawley (M)	Weanling	7–10	30 mg/kg bw MAM, s.c., killed 20 weeks after MAM	Dietary restriction: Natural ingredient diet fed 25% less of diet	DR day 10–140; DR day 63–140; AL/fasted alternate days for 8 days; AL/fasted alternate days for 31 days	Av. no. of tumours/ rat[4]: AL throughout, 1.4–2.7[b]; 25% DR day 10–140, 0.4[a]; 25% DR day 63–140, 2.2; AL/fasted alternate days 8 d, 1.1; AL/fasted alternate days 31 d, 2.0	DR throughout inhibited tumours	Pollard *et al.* (1984)
Fischer 344 (M)	Weaning	30	15 mg/kg bw AOM, s.c. x 2, at 7 and 8 wks. Killed at 32 weeks after AOM	Semipurified diet, HF and 30% ER	4 days after AOM until the end of experiment	Colon cancer incidence:[4] HF AL, 9%[b] ER, 0%[a]	ER of HF inhibited tumours	Reddy *et al.* (1987)
Charles River Sprague-Dawley (dams M/F offspring)	Birth	25–40 females and litters and 25–40 offspring	10 mg/kg bw DMH, s.c., 2 x wk for 10 wk, beginning 1 mo post weaning, killed 20 wks after last DMH	Semipurified diet, litter size adjusted to 4 or 8 pups/ litter	Before and after DMH	% colon tumours:[4] 8 pups/litter – M, 48%[a] and F, 42%[a]; 4 pups/ litter – M, 85%[b] and F, 60%[b]; 4 pups/ litter, birth–weaning, 76%[b]; pair-fed to 8 pups/litter after weaning, 52%	Reducing litter size enhanced tumours	Newberne *et al.* (1990)
Zucker *(fa/fa), (Fa/Fa)* and *(Fa/fa)* (M)	8	9–10	15 mg/kg bw AOM, s.c. at 10 and 11 wks killed at 12 wks after last AOM	Crude natural ingredient diet, LF, 10% calories from fat; HF, 40% calories from fat	Throughout	Tumour incidence[4]: *fa/fa* (obese) LF, 89%[b]; *Fa/Fa* (lean) HF, 0%[a]; *Fa/fa*, LF, 0%[a]; *Fa/fa* HF, 0%[a]	Obesity phenotype increased tumours	Weber *et al.* (2000)

Table 46 (contd)

Organ site, species, strain (sex)	Age at beginning of study (wk)	No. of animals per group	Carcinogen/ dose/route	Dietary restriction/ amount, type	Timing of restriction	Prevention effect	Summarized effect	Reference
Mammary gland								
Mouse								
Pure bred (M/F)	Weanling	48–50	Spontaneous, killed at 100 wks of age	Cereal based (fox chow diluted with cornstarch, removed cornstarch for restriction): control 10–12 kcal/day; intermediate 8.2 kcal/day; low energy 7.1 kcal/day	Throughout	Tumour incidence: 10–12 kcal/day, 54% 8.2 kcal/day, 12%, 7.1% kcal/day, 0%	ER inhibited	Tannenbaum (1945)
C3H/HeOu (F)	4	24	Spontaneous, killed at 60 wks	Energy restriction: 0 (control) and 40% restriction; energy restricted by reducing calories from protein and carbohydrate	From 5 up to 40%: control ER, 60 wks ER, wks 4–12 of age	% mammary tumour-free[3]: 17%[c] 87%[b] 50%[a]	ER late in promotion inhibited	Engelman *et al.* (1994)
			Spontaneous, longevity study	40% DR with vitamin supplementation	From 16 weeks throughout	Tumour (benign and malignant) incidence:	DR decreased tumours	Sheldon *et al.* (1996)
$B6C3F_1$ (F)	4	55				Control 13%; DR 2%		
$B6D2F_1$ (F)	4	56				Control, 15%; DR, 0%		
C57BL/6 (F)	4	37				Control, 5%; DR, 0%		
Rat								
Sprague-Dawley (F)	50 days	17–18	5 mg DMBA, i.v. at 57 days of age, killed at 26 wks	Cereal-based diet, 50% diet restriction	Diet restricted 7 d before and 30 d after DMBA treatment	Mammary tumour incidence:[4] Control, 76%[b] DR, 29%[a]	DR around DMBA inhibited tumours	Sylvester *et al.* (1981)
Sprague-Dawley (F)	50 days	[18–21]	5 mg DMBA, i.v. at 57 days of age, killed at 21 wks	Cereal-based diet, 50% diet restriction	Diet restricted 1 wk before and 1 wk after DMBA treatment, or for 2 wks starting 1, 3 wks after after DMBA, or for 4 wks starting 5 wks after DMBA	Mammary tumour incidence[4]: Control, 81%[b]; diet restricted 1 wk after DMBA treatment, 28%[a] or for 2 wks starting 1, 76%, 3, 75% after DMBA, or for 4 wks starting 5 wks,	Only ER 1 wk before and 1 wk after DMBA inhibited tumours	Sylvester *et al.* (1982)

Table 46 (contd)

Organ site, species, strain (sex)	Age at beginning of study (wk)	No. of animals per group	Carcinogen/ dose/route	Dietary restriction/ amount, type	Timing of restriction	Prevention effect	Summarized effect	Reference
Fischer 344 (F)	52 days	14–15	65 mg/kg bw DMBA by gavage, killed at 24 wks after DMBA	Control semi-purified (5% fat), HF (30% fat), HF restricted to the net energy value consumed by the control group (HFR)	Beginning one day after DMBA	Cumulative adeno-carcinoma incidence: Control, 40% HF, 73% HFR, 8%	Restriction of HF diet inhibited tumours	Boissonneault *et al.* (1986)
Sprague-Dawley (F)	50 days	20	5 mg DMBA by gavage, killed at 20 wks	Energy restriction: 0 (control), 10, 20, 30, and 40% restriction	Throughout	Tumour incidence[4]; Control, 60%[b]; 10% ER, 60%; 20% ER, 40%[a]; 30% ER, 35%[a]; 40% ER, 5%[a]	Dose–response inhibition with ER	Klurfeld *et al.* (1989a)
Sprague-Dawley (F)	50 days	20	5 mg DMBA by gavage, killed at 20 wks	Energy restriction: 0 (control) and 25% restriction	Beginning one week after DMBA: control ER, 4 mo ER, 1 mo/C, 3 mo ER, 2 mo/C, 2 mo C, 1 mo/ER, 2 mo/C, 1 mo C, 2mo/ER 2 mo	Cumulative incidence of palpable tumours: 50% 20% 60% 40% 45% 30%	ER late in promotion inhibited tumours	Kritchevsky *et al.* (1989)
Sprague-Dawley (F)	50 days	10–80	5 mg DMBA by gavage, killed at 20 wks after feeding regimens	Energy restriction: 0 (control) 25 and 40% restriction	Beginning one week following DMBA	Tumour incidence[5]: Control, 90%*; 25% ER, 61%*; 40% ER, 20%*	Dose–response inhibition with ER	Ruggeri *et al.* (1989)
LA/N phenotypically lean or obese (F)	65 days	15 pairs obese and 19 pairs lean	5 mg DMBA by gavage, killed at 16 wks	Energy restriction: 0 (control) and 40% restriction	Beginning one week after DMBA: control, obese ER, obese Control, lean	Cumulative incicidence of palpable tumours 100% 27% 21%	ER of obese inhibited tumours	Klurfeld *et al.* (1991)

Table 46 (contd)

Organ site, species strain (sex)	Age at beginning of study (wk)	No. of animals	Carcinogen/ dose/route	Dietary restriction/ amount type	Timing of restriction	Prevention effect	Summarized effect	Reference
Sprague-Dawley (F)	50 days	20	25 mg/kg bw MNU, i.v., killed at 20 wks	Energy restriction: 0 (control) and 30% restriction	Beginning one day after MNU: all rats fed 50 kcal/day/45% fat diet (control/HF) until tumours were 1 cm^3, then some were fed for 10±2 weeks on this diet: 35 kcal/day/45% fat (ER/HF), 50 kcal/day/25% fat (control/LF), 35 kcal/day/25% fat (ER/LF)	Tumour/body weight (%): ER/HF, 2.2; Control/LF, 2.5; ER/LF, 1.3	ER of LF or HF inhibited tumours	Zhu *et al.* (1991)
Fischer 344 (F)	4	54–180	Spontaneous longevity study	40% DR with vitamin supplementation	From 16 weeks throughout	Adenocarcinoma incidence: Control, 6%; DR, 1%	DR decreased tumours	Thurman *et al.* (1994)
Fischer 344 (F)	50 days	30–32	50 mg/kg bw MNU, i.p., x 2, 50 and 57 d, killed at 20.5 wks after MNU	Meal-fed control semi-purified diet and 20% ER	Beginning at 64 d of age, with or without exercise (progressively up to running 20 m/min at 15% grade for 30 min, 5 days/wk)	Cumulative adenocarcinoma incidence:[4] Control, sedentary, 23%[b]; ER, sedentary, 7%[a], control, exercise, 28%[b]; ER, exercise, 34%[b]	ER or sedentary inhibited tumours	Gillette *et al.* (1997)
Sprague-Dawley (F)	21 days	24	50 mg/kg bw MNU, i.p., killed at 35 days after MNU	Energy restriction: 0 (control) 10, 20 and 40% restriction	Following carcinogen treatment to end of study	Proportion of carcinoma[5]: Control, 4.55%*; 10% ER, 2.72%*; 20% ER, 1.76%*; 40% ER, 0.29%*	Dose–response inhibition of tumours	Zhu *et al.* (1997)

Table 46 (contd)

Organ site, species, strain (sex)	Age at beginning of study (wk)	No. of animals per group	Carcinogen/ dose/route	Dietary restriction/ amount, type	Timing of restriction	Prevention effect	Summarized effect	Reference
ACI	7	21	17β-Estradiol (E2) in silastic tubing implants from 8.5 wks, killed when tumours were 1.5–2.0 cm diameter or at 220 days of E2	Energy restriction: 0 (control) and 40% ER from fat and carbohydrate	Throughout	Mammary cancer incidence at end of study in E2-treated groups:[4] Control, 100[b] ER, 60%[a]	ER inhibited tumours	Harvell *et al.* (2001a)
Prostate								
Rat								
Lobund Wistar germ-free and conventional (M)	Weanling	100	Spontaneous, killed at 6, 18, 30 or 30+ months	Cereal-based diet; diet restricted 30%	Throughout	Prostate adenocarcinoma: Control-conventional, 26%; DR-conventional, 6%; control-germ-free, 5%; DR-germ-free, 10%	DR inhibited tumours in conventional rats	Pollard *et al.* (1989)
Pancreas								
Rat								
Lewis (M)	2	22–24	30 mg/kg bw azaserine x 1 i.p., at suckling, killed at 14 mo after azaserine	Meal fed: AL 5–6 h day	For the first two months after initiation, for the second two months after initiation or for 4 months after initiation	Carcinoma incidence[2]: control, 65%[c]; MF/C, 26%[b]; C/MF, 21%[b]; MF/MF, 0%[a]	Meal feeding for 4 months inhibited more than meal feeding during 2 months in early or late promotion	Roebuck *et al.* (1993)
Hamster								
Syrian golden (M)	8	25–35	20 mg/kg bw BOP x 1, s.c., killed at 94 wks	AL (av., 29–35 kcal /day); 'control fed' (av., 27 kcal/day); with control diet (4.3% fat) or high fat (20.5% fat)	1 week after initiation	Ductular carcinoma incidence[3]: AL/ control, 8%[a]; AL/HF, 30%[b]; control fed/control, 13%[c]; control fed/ HF, 52%[d]	HF diet increased tumours	Birt *et al.* (1989)

Table 46 (contd)

Organ site, species, strain (sex)	Age at beginning of study (wk)	No. of animals per group	Carcinogen/ dose/route	Dietary restriction/ amount, type	Timing of restriction	Prevention effect	Summarized effect	Reference
Syrian golden (M) (M)	8	33–38	20 mg/kg bw BOP weekly, x 3 s.c., killed at 42–44 wks after last BOP	Control, 20 and 40% ER from fat and carbohydrate	After initiation	No. of carcinomas/ effective animals[4]: control, 0.9[a]; 20% restricted, 1.2; 40% 1.7[b]	40% ER increased multiplicity	Birt *et al.* (1997)
Skin								
Mouse								
Rockland (F)	8–12	48	Benzo[*a*]pyrene; 60 µg 2 x wk, 38 weeks, terminate at 38 week, topical	50% ER, removal of carbohydrate	Throughout	Tumour incidence: control, 82%; 50% restriction, 16%	ER reduced tumours	Boutwell *et al.* (1949)
Sencar (F)	9	23–30	10 nmol DMBA x 1 + 3.2 nmol TPA, 2 x wk, 20 weeks, topical, killed at 50 wk	40% restriction, removal of fat and carbohydrate (ER) or feeding less diet (DR)	Restriction only before DMBA or only after DMBA	Carcinoma incidence[4]: control, 71%[b]; ER before, 69%; DR before, 58%; ER after, 28%[a]; DR after, 41%	ER inhibited more than DR	Birt *et al.* (1991)
Sencar (F)	9	45	10 nmol DMBA x 1 + 3.2 nmol TPA, 2 x wk, 20 weeks, topical, killed at 59 wks after DMBA	35% ER, removal of fat or carbohydrate	Restriction during and after TPA	Carcinoma incidence[4]: control 70%[b]; removal of fat, 45%[a]; removal of carbohydrate, 45%[a]	ER from fat or from carbohydrate inhibited	Birt *et al.* (1993)
Sencar (F)	9	31–48	10 nmol DMBA x 1 + 3.2 nmol TPA, 2 x wk, 2 weeks, then 10 nmol Mezerein 2 x wk, 16 weeks, topical, killed at 62 wk after DMBA	40% energy restriction from fat and carbohydrate	Restriction during TPA, or during Mezerein or during both exposure periods	Carcinoma incidence[1]: control, 29%[f]; ER during TPA, 33%[f]; ER during Mezerein, 15%[e]; ER during both, 10%[e]	ER during late promotion or throughout inhibited	Birt *et al.* (1994a)

Table 46 (contd)

Organ site, species, strain (sex)	Age at beginning of study (wk)	No. of animals per group	Carcinogen/ dose/route	Dietary restriction/ amount, type	Timing of restriction	Prevention effect	Summarized effect	Reference
Sencar (F)	9	35	10 nmol DMBA x 1 + 3.2 nmol TPA, 2 x wk, 18 weeks topical, killed at 45 wk after DMBA	20 and 40% ER from fat and carbohydrate from LF (10% fat) or HF (42% fat) diets	Restriction during and after TPA	Carcinoma incidence[1]: Control, 40%[d]; 20% restriction from LF, 40% restriction from LF, 15%[c]; HF, 35%[b]; 20% restriction from HF, 35%; 40% restriction from HF, 0%[a]	LF diets: 20% ER and 40% ER inhibited; HF diets: only 40% ER inhibited	Birt *et al.* (1996)
Liver								
Mouse								
Swiss OF1 (M/F)	Weanling	14–17	0.4 µmol/g bw DEN, i.p. killed at 48 wk	Cereal-based diet, 30% DR	*Ad libitum* throughout DR thoughout AL-36 wk/DR-12 wk DR-36 wk/AL-12 wk	Incidence of hepatocellular adenoma or carcinoma AL throughout 14%[b] DR throughout 10%[a] AL-36 wk/DR-12 wk 14% DR-36 wk/AL-12 wk 13%	DR throughout inhibited	Lagopoulos *et al.* (1991)
$B6C3F_1$	4		Spontaneous, longevity study	40% DR with vitamin supplementation	From 16 weeks throughout	Tumour (benign and malignant) incidence Control, 39%; DR, 9%; Control, 11%; DR, 11%	DR decreased tumours	Sheldon *et al.* (1996)
(M)		56						
(F)		56						
$B6D2F_1$	4							
(M)		56				Control, 24%; DR, 2%		
(F)		56				Control, 13%; DR, 4%		
C57BL/6	4							
(M)		50				Control, 12%; DR, 0%		
(F)		37				Control, 3%; DR, 0%		
Pituitary gland								
Mouse								
$B6C3F_1$ (F)	4	55	Spontaneous, longevity study	40% DR with vitamin supplementation	From 16 weeks throughout	Adenoma incidence: Control, 30%, DR, 0%	DR decreased tumours	Sheldon *et al.* (1996)

Table 46 (contd)

Organ site, species strain (sex)	Age at beginning of study (wk)	No. of animals pergroup	Carcinogen/ dose/route	Dietary restriction/ amount, type	Timing of restriction	Prevention effect	Summarized effect	Reference
$B6D2F_1$ (F)	4	56				Control, 17%; DR 0%		
C57BL/6 (F)	4	37				Control, 57%; DR, 2%		
Rat								
Fischer 344 (M)	4	54–180	Spontaneous longevity study	40% DR with vitamin supplementation	From 16 weeks throughout	Tumour incidence; Control, 72%; DR 36%	DR decreased tumours	Thurman *et al.* (1994)
Fischer 344 (F)	4					Tumour incidence: Control, 74%; DR, 44%		
Fischer 344			17β-Estradiol in silastic tubing implants for 12 wks	40% energy restriction from fat and carbohydrate	Throughout	Fold induction of pituitary weight by E2 compared with untreated rats:[4] Control, 5x[b]; 40% ER, 2 x[a]	ER reduced adenoma	Harvell *et al.* (2001b)
Copenhagen			17β-Estradiol in silastic tubing implants for 12 wks	40% energy restriction from fat and carbohydrate	Throughout	Fold induction of pituitary weight by E2 compared with untreated rats:[4] Control, 2.5x[b]; 40% ER, 1.5x[a]	ER reduced adenoma	Harvell *et al.* (2001b)
ACI			17β-Estradiol in silastic tubing implants for 12 wks	40% energy restriction from fat and carbohydrate	Throughout	Fold induction of pituitary weight by E2 compared with untreated rats:[4] Control, 3.5 [a]; 40% ER, 4.5x[b]	No effect of ER	Harvell *et al.* (2001b)

Table 46 (contd)

Organ site, species, strain (sex)	Age at beginning of study (wk)	No. of animals per group	Carcinogen/ dose/route	Dietary restriction/ amount, type	Timing of restriction	Prevention effect	Summarized effect	Reference
Lymphoma								
Mouse								
$B10C3F_1$ (M)	45–50	67–68	Spontaneous, killed when moribund	Semipurified diet DR with supplementation: Control (160 kcal/wk) DR (90 kcal/wk)	Diet initiated at 12–13 mo of age	Tumour incidence[4]: Control, 47%[b]; DR, 31%[a]	DR inhibited	Weindruch & Walford (1982)
C57BL/6 (M)	45	60–72	Spontaneous, killed at 25 mo of age	ER, 25%	Diet initiated at 12 mo of age	Tumour incidence[4]: Control, 19%[b]; DR, 5%	DR inhibited	Volk *et al.* (1994)
$B6C3F_1$	4		Spontaneous, longevity study	40% DR with vitamin supplementation	From 16 wks throughout	Tumour incidence:	DR decreased tumours	Sheldon *et al.* (1996)
(M)		56				Control, 41%; DR, 11%;		
(F)		56				Control, 61%; DR, 29%		
$B6D2F_1$	4							
(M)		56				Control, 38%; DR, 29%		
(F)		56				Control, 36%; DR, 21%		
C57BL/6	4							
(M)		50				Control, 8%; DR, 7%		
(F)		37				Control, 30%; DR, 9%		
C57BL/6 & 129/Sv *p53*$^{-/-}$ *p53*$^{+/+}$	Weanling	28–30	Spontaneous, genetically engineered mouse *p53*$^{-/-}$, killed when moribund	Semi-purified energy restricted by 40% reduction from carbohydrate	Throughout	Time to death (tumour mortality) *p53*$^{-/-}$/control, 110 days *p53*$^{-/-}$/ER, 162 days *p53*$^{-/-}$/control, 384 days; *p53*$^{-/-}$/ER, 643 days	ER increased time to death	Hursting *et al.* (1997)

AL, *ad libitum*; AOM, azoxymethane; BOP, *N*-nitrosobis-(2-oxopropyl)amine; C, carcinogen; DMBA, 7,12-dimethylbenz[*a*]anthracene; i.m., intramuscular, i.p., intraperitoneal; i.v., intravenous; DMH, 1,2-dimethylhydrazine; DR, dietary restriction; ER, energy restriction, HF, high fat; LF, low fat; MAM, methylazoxymethanol; MF, meal fed; MNU, *N*-methyl-*N*-nitrosourea; s.c., subcutaneous; TPA, 12-*O*-tetradecanoylphorbol 13-acetate

[1]Statistically significant differences: pooled e < pooled f

[2]Statistically significant differences: a < b < c

[3]Statistically significant differences: a < b; c < d

[4]Statistically significant differences: a < b

* Significant trend

intake of the animals in the group with eight per litter, had intermediate cancer rates. The rats in litters of eight had the lowest rates. In a recent study on the relationship of obesity and high-fat diet to colon cancer, AOM induced large colon cancers in 8 out of 9 genetically obese Zucker rats (*fa/fa*) fed a low-fat diet, while parallel groups consisting of their genetically lean genotypes (*Fa/Fa* and *Fa/fa*) developed no gross lesions (Weber *et al.*, 2000). Furthermore, more colon aberrant crypts were observed in the obese Zucker rats fed low-fat diet than in the lean counterparts fed low- or high-fat diet.

Mammary gland

The most extensively studied organ system for cancer-preventive effects of dietary energy restriction is the mammary gland. Mammary carcinogenesis induced by viruses in mice or by chemical carcinogens such as 7,12-dimethylbenz[*a*]anthracene (DMBA), *N*-methyl-*N*-nitrosourea (MNU) and benzo[*a*]pyrene (BP) in mice and rats is inhibited by energy restriction (Freedman *et al.*, 1990; Decarli *et al.*, 1997; Kritchevsky, 1997). In general, mammary carcinomas induced in mice are alveolar in origin and are not dependent on ovarian steroids for their development and growth. For this reason, the majority of studies reviewed in this section were selected because they used one of two chemical carcinogens which induce mammary cancers that have many characteristics similar to the human counterparts. These characteristics include: ductal origin, ovarian hormone dependence and morphology.

Recent studies to assess the effect of energy restriction on mammary carcinogenesis have differed in strategy in various ways: restricting diet to different extents, feeding during different phases of cancer development, comparing the sources of energy or assessing the relation of body fatness to cancer prevention. Two related strategies that are covered elsewhere are comparing the effects of reduced calorie availability by dietary or energy restriction with those of increased energy use through an exercise regimen (covered in the next section of this chapter) and cyclic feeding, which results in a reduction in or loss of the protection due to restriction and is therefore covered in Chapter 7. Furthermore, several investigations have attempted to link changes in body composition with underfeeding and cancer prevention.

Tannenbaum (1945) investigated the influence of the level of energy restriction on spontaneous mammary cancer in mice. He noted that a reduction in daily energy intake from 12 to 7 calories [from 50 to 29 J] completely eliminated spontaneous mammary tumours, while the mean age at death of the non-tumour-bearing mice increased from 76 ± 5.1 weeks to 83 ± 2.8 weeks. Klurfeld *et al.* (1989a) compared rats subjected to 10, 20, 30 or 40% energy-restriction with freely fed controls and found a slight reduction in DMBA-induced mammary cancer incidence and multiplicity with 20% restriction and significant inhibition with 30 or 40% energy restriction. Reduced body weight and body fat were correlated with the reduction in tumour weight. Similar results were obtained by Ruggeri *et al.* (1989), but while inhibition of mammary carcinogenesis with 40% energy restriction was significantly correlated with reduced levels of circulating insulin, a reduction in carcinogenesis with 25% energy restriction was not paralleled by a significant reduction in circulating insulin (discussed further in the section on mechanisms later in this chapter). In a longevity study on Fischer 344 rats, 40% energy restriction also decreased the incidence of spontaneous adenoma and adenocarcinomas (Thurman *et al.*, 1994). Zhu *et al.* (1997) observed dose-related inhibition of mammary carcinogenesis, in terms of both incidence and multiplicity, in rats treated with 50 mg/kg bw MNU followed by an observation period of 35 days. Dramatic inhibition by 10, 20 or 40% energy restriction was seen in this rapid mammary tumorigenesis model, in comparison with freely fed controls, and the inhibition correlated with elevated excretion of corticosterone. Indeed, corticosterone excretion could serve as an independent predictor of the animal's cancer response in this study (Zhu *et al.*, 1997).

The impact of dietary or energy restriction during different stages of mammary carcinogenesis has also been assessed (Sylvester *et al.*, 1981, 1982; Kritchevsky *et al.*, 1989; Engelman *et al.*, 1994). Sylvester *et al.* (1981) studied the effect of short-term dietary restriction (50%) on DMBA-induced mammary carcinogenesis. They found that restriction for seven days before and for 30 days after treatment with the carcinogen resulted in a significant reduction in the average number of carcinomas by the end of a 26-week experiment. Short-duration under-feeding one week before and one week after DMBA treatment decreased tumour incidence, but underfeeding for two weeks beginning one or three weeks after treatment or for four weeks starting five weeks after treatment failed to inhibit the carcinogenic response as assessed 21 weeks later (Sylvester *et al.*, 1982). Kritchevsky *et al.* (1989) treated rats with DMBA and restricted their energy intake by 25% at different times during the next four months. The animals were placed on restricted energy during all the four months, during the first one or two months of this period, during the middle two months or during the last two months. Energy restriction reduced mammary cancer rates when applied throughout the four months or when initiated late in the process, but was not effective when administered early followed by *ad libitum* feeding (Kritchevsky *et al.*, 1989). These results showed that inhibition of the carcinogenic process was dependent on the time-frame over which energy restriction was imposed,

the duration of energy restriction and the proximity of the energy restriction to the termination of the study. Engelman *et al.* (1994) examined the effect of the time of energy restriction (5–40% restriction) on spontaneous mammary cancer in C3H/HeOu mice. Mice were subjected to energy restriction from four weeks until the end of the study at 60 weeks of age or from weeks 4 to 12 followed by *ad libitum* feeding. The reduction in cancer was greatest with energy restriction throughout the study (about 90% of mice tumour-free at 60 weeks), intermediate with energy restriction from weeks 4–12 (about 50% of mice tumour-free at 60 weeks of age) and least in controls (17% of mice tumour-free at 60 weeks of age) (Engelman *et al.*, 1994). These observations were paralleled by reduction of numerous indices of mammary gland development by energy restriction. Reduction of tumour incidence by 40% dietary restriction was also observed in several strains of mice by Sheldon *et al.* (1996).

From a review of the literature and by comparing the effects of reductions in dietary fat with those of reductions in dietary energy intake, Freedman *et al.* (1990) concluded that both high-energy and high-fat diets increased mammary tumour incidence, with the magnitude of the effect of fat being two thirds that of energy. They further summarized data showing that the enhancement by dietary fat of mammary tumorigenesis was not simply due to elevations in body weight, but that there was a "specific enhancing effect of dietary fat" on mammary carcinogenesis. Ip (1990) observed the greatest reduction in mammary cancer when both fat and energy were reduced. Boissonneault *et al.* (1986) studied the influence of fat and energy intake on mammary carcinogenesis in DMBA-treated Fischer 344 rats. They calculated relative net energy values and restricted the intake of a high-fat diet (30%) to the net energy intake of the low-fat group (5%). Carcass energy was highest in the high-fat group, intermediate in the high-fat restricted (HFR) group and lowest in the low-fat group, while the mammary cancer incidence was lowest in the HFR group. It was concluded that mammary cancer development was related to a complex interaction of energy intake, energy retention and body size rather than to the percentage of fat in the diet. Zhu *et al.* (1991) assessed the effects of dietary fat and dietary energy on the growth of established mammary tumours in Sprague-Dawley rats. Mammary cancers were induced with 25 mg/kg MNU at 50 days of age and when tumours reached 1 cm^3, the rats were fed diets containing 25% or 45% dietary fat either *ad libitum* or with 30% energy restriction. Tumour growth was lowest in the low-fat 30% energy-restricted group. Reductions in fat intake did not significantly inhibit tumour growth.

The importance of body fat for mammary carcinogenesis has been evaluated. Studies with reduced energy intake after DMBA treatment comparing genetically obese LA/N-cp female rats with phenotypically lean littermates suggested that body fatness *per se* was not directly related to the risk of mammary carcinogenesis (Klurfeld *et al.*, 1991). In fact, energy restriction of the obese rats reduced lean body mass more than body fatness. Gillette *et al.* (1997) subjected rats treated with MNU (50 mg/kg at 50 and 57 days of age) to a treadmill-exercise regimen (20 m/min at a 15% grade for 30 min on five days per week) with or without energy restriction (20% reduction). Body weight gain, carcass fat and carcass energy were reduced in the exercised and energy-restricted groups, but mammary carcinogenesis was inhibited only in the sedentary energy-restricted rats. This finding is consistent with that of Klurfeld *et al.* (1991), indicating that carcass fat *per se* was not directly associated with cancer risk.

Recent studies of 17β-estradiol-induced mammary cancer in the ACI rat have demonstrated marked inhibition by dietary energy restriction of mammary cancers but no prevention of 17β-estradiol-induced focal regions of atypical hyperplasia and no alteration in circulating estradiol (Harvell *et al.*, 2001a). This suggests that energy restriction may inhibit tumour development by blocking the progression of hyperplasia to mammary cancers.

Prostate

Pollard *et al.* (1989) examined spontaneous tumours in the prostate, liver and adrenal glands of conventional and germ-free Lobund-Wistar rats. A 30% reduction in dietary intake reduced prostate tumours from 25.7% to 6.3% and extended latency from 26.6 months to 36.7 months in conventional rats. The spontaneous prostate tumours were squamous-cell carcinomas, unlike the prostate adenocarcinomas observed in humans. In this study, although spontaneous liver adenomas were inhibited by reduced dietary intake, adrenal adenomas were not.

Pancreas

The effect of modifying energy intake has been assessed using two models of pancreatic cancer, azaserine-induced acinar carcinogenesis and BOP-induced ductular carcinogenesis. Azaserine induces acinar-cell acidophilic foci acinar carcinomas. Although such lesions are seen in human pancreas, acinar carcinomas account for a minor fraction of human pancreatic cancer. In contrast, BOP-induced pancreatic ductular carcinoma is highly representative of the human disease (Pour *et al.*, 1993). Using the azaserine model, Roebuck *et al.* (1993) demonstrated that meal feeding of rats for 5–6 h/day (matching a 10–15% energy restriction) resulted in an approximately 40% reduction in carcinoma incidence. Birt *et al.* (1989, 1997) fed restricted intakes to Syrian golden hamsters as part of a study of the impact of dietary fat on carcinogenesis. A delay of about eight weeks was observed in

the induction of ductular pancreatic cancer by BOP in the 'control-fed' high-fat group compared with the *ad-libitum*-fed high-fat group. The reduction in dietary intake in the 'control-fed' high-fat hamsters compared with the *ad-libitum*-fed high-fat hamsters was about 23% (Birt *et al.*, 1989). Since this suggested that energy restriction delayed pancreatic carcinogenesis, the second study assessed the impact of 10, 20 and 40% dietary energy restriction on pancreatic carcinogenesis by BOP (Birt *et al.*, 1997); no inhibition of ductular pancreatic carcinogenesis was detected, and in contrast, a nearly twofold increase was seen in the multiplicity of pancreatic ductular carcinogenesis in the 40% dietary energy-restricted hamsters (see section on mechanisms later in this chapter).

Skin

The two-stage model of skin carcinogenesis has been particularly useful in assessing the inhibition of carcinogenesis by dietary energy restriction because of the ability to separate effects on initiating events from those on promoting events and because of the wealth of information available on the biochemical processes and the gene mutations that are important in carcinogenesis in this model. While chemically induced skin cancers are a good model of epithelial carcinogenesis, they do not well resemble human skin cancers, which are induced primarily by ultraviolet light. Boutwell *et al.* (1949) demonstrated that enhancement of BP-induced skin carcinogenesis by high levels of dietary fat was dependent upon the higher energy intake of the mice. More recent studies by Birt and colleagues have been reviewed (Birt *et al.*, 1995). Energy restriction was effective in protecting against skin carcinogenesis induced by DMBA and promoted by 12-*O*-tetradecanoylphorbol 13-acetate (TPA) when restriction was implemented during promotion, but was not effective when given for a short time before and during the initiation phase (Birt *et al.*, 1991). Restriction either of fat plus carbohydrate energy or of all dietary constituents during skin tumour promotion resulted in fewer papillomas and carcinomas, but selective restriction of fat and carbohydrate energy gave greater inhibition of papilloma growth, papilloma number and carcinoma incidence than diet restriction (Birt *et al.*, 1991). Furthermore, while high dietary fat intake did increase skin carcinogenesis, reductions in energy intake were much more potent in inhibiting carcinogenesis (Birt *et al.*, 1993). In particular, restricting carbohydrate energy was more effective than restricting fat energy in the prevention of skin papillomas, although these two dietary restriction protocols were equally effective in preventing development of DMBA-initiated, TPA-promoted squamous cell carcinomas in Sencar mice. Restricting mice to either 20 or 40% of the energy intake of freely fed controls reduced the incidence of skin carcinomas by more than 50% in mice on a control fat (10% of energy) diet, while 40% energy restriction, but not 20% energy restriction, was effective in preventing skin cancer in mice fed high-fat (42% of energy) diets (Birt *et al.*, 1996). Studies with a two-stage promotion model using TPA as an early-stage promoter (two weeks) or mezerein as a late-stage promoter (16 weeks) showed that energy restriction was most effective in inhibiting late-stage promotion (Birt *et al.*, 1994a).

Liver

Chemically induced and spontaneous liver tumours in rodents are considered to model those occurring in humans because of their close similarity in morphological appearance (Scarpelli, 1988). Furthermore, rodent liver tumours often metastasize to the lung, as occurs in humans. Dietary energy restriction for prevention of liver carcinogenesis has been studied in animal models. For example, Lagopoulos *et al.* (1991) examined liver tumours induced in mice by diethylnitrosamine (DEN) and demonstrated reductions in numbers of basophilic foci, adenomas and hepatocellular carcinoma after dietary restriction. *Ad libitum* feeding after long-term restriction resulted in the resumption of hepatic carcinogenesis and restriction was most effective when administered early in life. However, the mice fed restricted diets for 12 or 24 weeks followed by *ad libitum* feeding developed fewer hepatic lesions than the fully fed positive control group.

Liver tumours are often induced in chronic toxicity studies. Dietary restriction, used to achieve body weight control, reduced the incidence of both spontaneous liver tumour incidence and salicylazosulfapyridine-induced liver tumours (Iatropoulos *et al.*, 1997). Moreover, the incidences of liver tumours of unknown etiology (spontaneous) in rodents are also correlated with resultant body weight. In an analysis of over 100 chronic bioassays conducted by the US National Toxicology Program, from 75 to 90% (depending on study type) of the variance in control tumour (adenoma plus carcinoma) incidences (which ranged from 20 to 90%) was accounted for by variations in average body weight at approximately 14 months of age (Turturro *et al.*, 1996). Individual animal body weight at the same age was directly related, in an approximately quadratic relationship, to the probability of developing a tumour (liver, mammary, etc.) by the end of a toxicity test (Seilkop, 1995). [The Working Group noted that the potential role of genetic factors in accounting for these relationships was not considered.]

Direct modification of dietary intake, e.g., by dietary restriction, also inhibited spontaneous liver tumour incidences. A 40% dietary restriction (with supplementation) resulted in a reduction of tumour incidence in several mouse strains (Sheldon *et al.*, 1996). Changes in liver

physiology occur as a result of dietary restriction. In histological sections from animals sacrificed during the course of this study, the incidence of apoptosis in liver parenchymal cells was elevated and the estimated cellular proliferation rate decreased throughout the lifespan, compared with *ad libitum*-fed controls (Muskhelishvili *et al.*, 1995).

Pituitary gland

Dietary restriction has long been known to reduce the incidence of these usually benign but commonly fatal tumours in Sprague–Dawley rats (Everitt *et al.*, 1980). The tumours show many of the same characteristics as human tumours, with similar cell types affected. Dietary restriction also lowers the incidence of these lesions in Fischer 344 rats (Shimokawa *et al.*, 1991; Thurman *et al.*, 1994) and mice (Sheldon *et al.*, 1996).

The correlation of early dietary restriction and pituitary tumour incidence accounted for approximately half the variance in the wide range of pituitary tumour incidences (10–60%) in National Toxicology Program studies (Turturro *et al.*, 1998), while there was a direct relationship between individual animal body weight and the probability of developing a pituitary tumour in long-term chronic studies (Seilkop, 1995).

Estrogen-induced prolactin-producing pituitary tumours that are observed in rats are markedly enlarged benign masses that display diffuse lactotroph hyperplasia and hypertrophy. They are highly vascularized but generally lack adenomatous foci (Spady *et al.*, 1999). In humans, the majority of pituitary tumours are microadenomas, usually composed of a single secretory cell type. Prolactin-producing pituitary tumours, referred to as prolactinomas, are the most frequently occurring neoplasm in the human pituitary. Several case reports suggest that estrogens act as a causative factor in the development of prolactinomas in humans. Similarities in the manner in which pituitary cells of the prolactin-producing cell type respond to estrogen in rats and humans suggest that estrogen is a risk factor for pituitary tumour development in both species.

The effect of 40% energy restriction on estrogen-induced pituitary adenomas was assessed in three rat strains: Fischer 344, Copenhagen and ACI (Harvell *et al.*, 2001b). Pituitary wet weight, commonly used as an indicator of pituitary tumorigenesis, was increased by estrogen in all strains and energy restriction reduced this increase in Fischer 344 and Copenhagen rats but not in ACI rats. Therefore, genetic background may be an important determinant in prevention of pituitary tumours by energy restriction.

Lymphomas

A series of investigations of tumours of unknown etiology (spontaneous) determined that dietary restriction beginning during mid-life was effective in preventing spontaneous lymphomas in $B10C3F_1$ mice (Weindruch & Walford, 1982). Lymphomas were significantly reduced in number and delayed in occurrence, although hepatomas were equally prevalent in the underfed and control-fed groups. Similarly, fewer lymphomas were found in energy-restricted C57BL/6 mice and this was paralleled by inhibition of age-associated interleukin-6 (IL-6) dysregulation, including prevention of the increasing serum level of IL-6 observed in control mice (Volk *et al.*, 1994). Reduction of spontaneous lymphomas by 40% dietary restriction in mice has also been demonstrated (Sheldon *et al.*, 1996).

Other tumours

Inhibition due to dietary restriction (with vitamin supplementation) has been observed for a number of other tumours in rodents. These include: thyroid follicular tumours in mice, which are similar to the follicular form seen as the minority of human thyroid cancers (which are mostly of the papillary type) (Sheldon *et al.*, 1996; Hill *et al.*, 1998); interstitial cell tumours of the testes in rats, which are similar to human Leydig cell tumours, both morphologically and in overall hormonal sensitivity (Thurman *et al.*, 1994; Cook *et al.*, 1999); preputial and clitoral gland tumours in rats, which are sebaceous gland tumours that appear to be most similar to skin and urogenital tumours in humans (Raso *et al.*, 1992); thyroid C-cell and adrenal phaeochromocytomas in rats, which can be good models for multiple endocrine neoplasia type 2 in humans (Schulz *et al.*, 1992; Thurman *et al.*, 1994) and affect cells that are smaller than the usual chromaffin cells seen in humans but are otherwise similar (Tischler *et al.*, 1996); and lung tumours in male $B6C3F_1$ and $B6D2F_1$ mice, which are excellent models of human tumours in both morphology and oncogene features (Malkinson, 1992; Sheldon *et al.*, 1996). A comprehensive, though dated, review of the effects of dietary restriction on tumour development is available (Weindruch & Walford, 1988).

Genetically engineered mouse models

New genetically engineered animal models have been developed to study the misregulation of specific genes singly and in combination during the carcinogenic process. Both transgenic and knock-out models can be used. In one such model, both allelic copies of the wild-type *p53* tumour-suppressor gene are deleted (knocked out). This model is considered to have relevance to human cancer in general because mutations of the *p53* gene are the most commonly observed mutation in human cancer (Mowat, 1998). The *p53*-deficient mice are extremely susceptible to spontaneous occurrence of tumours. Using this model, Hursting *et al.* (1997) studied the effect of energy restriction on genetically induced lymphoma. The fact that energy restriction inhibits cancer development in p53 knock-out mice ($p53^{-/-}$) and that

inhibition of genetically induced carcinogenesis was similar in p53 wild-type ($p53^{+/+}$) and in $p53^{-/-}$ mice demonstrates that cancer prevention by energy restriction is independent of the functional status of *p53*. The use of genetically engineered animals raises the possibility of looking at the effects of energy restriction on incidence of tumours that are normally rare but are increased in such animals.

Physical activity

Laboratory experiments in which animal models are used to investigate the relationship between physical activity and cancer prevention have the potential: (1) to identify the characteristics of physical activity or exercise that are most likely to be critical to cancer prevention in humans; (2) to define mechanisms and markers of those mechanisms that would allow monitoring of disease progression in human populations over a short time frame; (3) to identify physical activity or fitness-related biomarkers of the 'cancer-protected state', and (4) to identify potentially confounding variables, for example dietary factors, that might mask the protective effects of physical activity if their existence were unrecognized (see review by Thompson, 1997).

Physical activity model (voluntary)

In the context of experimental studies, physical activity can be defined as any voluntary movement of an animal in which the skeletal muscles contract resulting in a quantifiable expenditure of energy. This definition does not require that the physical activity be designed to improve fitness, nor does the activity need to be done in a regular, structured or repetitive manner. Physical activity can be distinguished from exercise in that efforts to increase physical activity do not require an intent to improve physical fitness (Caspersen *et al.*, 1985). Providing animals with free access to an activity wheel provides an excellent model for studying the effects of increased levels of physical activity. Because animals choose when to run in the wheel and this behaviour has been demonstrated to vary between animals, there is nothing planned or structured about the physical activity associated with free access to the running wheel. Thus free use of an activity wheel, because it is voluntary, meets the definition of physical activity, but not exercise, and this is consistent with the way investigators studying carcinogenesis have designed experiments involving wheel-running. The amount of wheel-running activity has been quantified in terms of distance run or energy expended, without any attempt to set fitness goals and/or to assess training effects. Providing animals with free access to activity wheels appears well suited to answering questions about physical activity and cancer, particularly the question of whether total cumulative physical activity is predictive of risk for cancer. Apart from the expense of obtaining a sufficient number of properly engineered activity wheels for conducting a carcinogenesis experiment, issues that need to be considered if this model is used are the general decline in activity observed in experiments of several months duration, and the behaviour of some animals that turn their wheels without actually running in them.

Exercise models (involuntary)

Exercise can be defined as planned, structured and repetitive activity with the intent to develop and/or maintain some defined attribute of physical fitness. Of the animal models which are most frequently used, running on a treadmill, motorized drum or wheel has the potential to satisfy this definition. If animals are to be exercised, the activity will inevitably be involuntary and will usually require some type of reinforcement, depending on the intensity and duration of the exercise. Concern has been expressed that reinforcement of exercise behaviour to maintain compliance is likely to be stressful. While this is clearly a possibility, it must also be recognized that all exercise involves the imposition of a stress on muscles in order to improve fitness. Thus stress is an inherent component of studying exercise; a greater difficulty lies in defining the chemical basis of the various components of stress induced when animals are exercised to achieve and maintain defined fitness goals.

There are three primary components of exercise that can be varied and that may have different effects relative to carcinogenesis. They are the intensity (work-rate), the duration (length per activity bout) and the frequency (times per week) of the activity performed.

The most widely used animal model of exercise is the running of rodents on a variable-speed, incline-adjustable treadmill. The use of such a treadmill permits great flexibility in studying the effects of exercise intensity, since both the incline and the belt speed can be altered to achieve a particular work rate. Use of a warm-up and a warm-down period in the training protocol can reduce physiological stress and avoid injury to the animals. Metabolic treadmills are available that permit the measurement of aerobic capacity throughout an experiment. This procedure requires minimal alteration of an animal's routine so that the process of assessment can guide the training programme without independently affecting study results. When a treadmill is used, the animals need to be continuously monitored to minimize the risk of injury and ensure adherence to the exercise training protocol.

Physical activity and exercise control conditions

Two important issues must be considered in determining what constitutes an appropriate control for animal experiments in which either physical activity or exercise is studied. The first relates to the use of 'sham' conditions for physical activity or exercise. When access to wheel-running is used as the model, the

general approach has been to house control animals in the same type of activity cage as the experimental animals, but to lock the wheel so that it does not rotate. For the treadmill model, handling and placing animals in a stationary or slowly moving treadmill has been successfully used as a sham control. The key point is to expose the sham control animals to a set of stimuli similar to those faced by the experimental group. A second critical element of control in such experiments is the exposure of all animals to the same overall levels of environmental activity, including that of research technicians conducting the work, related to the implementation of the physical activity or exercise protocol. Such factors can significantly influence the carcinogenic response in some target organs such as the mammary gland. The control of this situation is straightforward. All animals in such studies should be housed in the same room in which the physical activity or exercise is performed. While this approach can require review by an institution's animal care and use committee for an exception to standard operating procedures, it is essential that this aspect of methodology be considered in order to preserve the integrity of the experiment.

The body of experimental information regarding the influence of physical exercise on development of premalignant and malignant lesions in animal models is very limited. The following review is organized with reference to organs and tissues (Table 47). The growth of transplantable tumours in experimental animals is not considered, since these studies have limited relevance to the primary prevention of cancer (see Rusch & Kline, 1944; Hoffman *et al.*, 1962; Good & Fernandez, 1981).

Colorectum

In a study of the influence of physical activity on DMH-induced colon carcinogenesis in the rat, Andrianapoulos *et al.* (1987) found that animals that were allowed running-wheel activity showed a significant reduction in the incidence of colon tumours (exercise group, 54.5%; non-exercise group, 90%).

Reddy *et al.* (1988) assessed the effects of voluntary exercise on AOM-induced colon carcinogenesis in male Fischer 344 rats. At five weeks of age, animals were divided into two groups (sedentary and exercise) and fed AIN-76A semi-purified diet *ad libitum*. They received a subcutaneous injection of 15 mg/kg bw AOM at seven weeks of age and another one week later. Those in the exercise group were then placed in individual wheel-cage units while the sedentary group were housed in normal plastic cages. At 38 weeks after AOM treatment, body weights of the exercise and sedentary groups were similar. The incidence and multiplicity of colon adenocarcinomas, but not of adenomas, were significantly reduced by the exercise. Incidences of small intestinal carcinomas and of liver foci were also reduced.

Colbert *et al.* (2000a) examined the effect of exercise training on polyp development in a mutant mouse strain predisposed to multiple intestinal neoplasia (Min mouse). Three-week-old male and female heterozygotes were randomly assigned to control (10 males, six females) or exercise (11 males, 11 females) groups. In the first week, exercised mice were acclimatized to treadmill running at 10–18 m/min for 15–60 min per day on five days per week. From four to 10 weeks of age, mice ran at 18–21 m/min for 60 min. Control mice sat in Plexiglas lanes suspended above the treadmill for the same time periods. At 10 weeks of age, the mice were killed. There were no significant effects of exercise on the multiplicity of small intestine, colon or total intestinal polyps in the males and females combined ($p > 0.05$). Among the males, when analysed separately, there were fewer colon and total polyps in the exercised than in the control mice, although the difference was not statistically significant ($p = 0.06$).

Mammary gland

Thompson and co-workers (Thompson *et al.*, 1988, 1989b, 1995; Gillette *et al.*, 1997) studied the effects of exercise and its interaction with dietary factors on mammary carcinogenesis in the rat. In the first two studies, low-intensity and short-duration exercise was shown to enhance cancer incidence. These studies are reviewed in Chapter 7.

Female Fischer 344 rats were given intraperitoneal injections of 50 mg/kg bw MNU at 50 and 57 days of age and subjected to sham exercise or 35% and 70% maximal treadmill running intensity for 20 or 40 min per day on five days per week. Mammary cancer incidence and multiplicity was lower in all exercise groups compared with the sham controls. As the degree of protection was proportional to the exercise intensity, rather than its duration, the authors concluded that intensity may be the more important factor determining protective activity (Thompson *et al.*, 1995).

Gillette *et al.* (1997) concentrated on energy availability and mammary carcinogenesis, looking at effects of both energy restriction and exercise. Female Fischer 344 rats were given intraperitoneal injections of MNU (50 mg/kg bw at 50 and 57 days of age) and then randomized into four groups: (i) unrestricted, sedentary; (ii) energy-restricted, sedentary; (iii) unrestricted, exercised; (iv) energy-restricted, exercised. The mammary carcinoma incidence was significantly lower in the energy-restricted sedentary group than in all other groups. No effect of exercise was seen, despite significant reductions in carcass fat and carcass energy.

Cohen *et al.* (1988, 1991, 1993) reported on the influence of dietary fat, energy restriction and voluntary physical activity on MNU- and DMBA-induced mammary carcinogenesis in rats.

Table 47. Studies of prevention of spontaneous and carcinogen-induced tumours by physical activity and exercise in experimental animals

Organ site species/ strain (sex)	Age at beginning of the study (wk)	Study type	No. per group	Carcinogen exposure	Type of exercise	Results	Reference
Colon and small intestine							
Rat							
Sprague-Dawley (M)	5	Pre-/post-initiation	11–21	20 mg/kg bw DMH, 1 x wk, 6 weeks, i.p., killed 20 weeks after final DMH	Voluntary – wheel cage	Decrease	Andrianapoulos *et al.* (1987)
Fischer 344 (M)	7	Post-initiation	12–27	15 mg/kg bw AOM, 1 x wk, 2 weeks, s.c., killed 38 weeks after carcinogen	Voluntary – wheel cage	Decrease of adenocarcinomas	Reddy *et al.* (1988)
Mouse							
C57BL/6Min (M+F)	Weaning	Spontaneous	6–11	Killed at 10 weeks of age	Treadmill	No effect	Colbert *et al.* (2000a)
Mammary gland							
Mouse							
BALB/cMed (F)	8	Post-initiation	29–48	1 mg DMBA, 1 x wk, 6 weeks, p.o. killed at 44 weeks of age	Treadmill – rotating drum	Decrease with diet restriction and high fat	Lane *et al.* (1991)
Rat							
Fischer 344 (F)	7	Post-initiation	30–36	37.5 mg/mg bw MNU i.v., killed 20 weeks after carcinogen	Voluntary – wheel cage	Decrease	Cohen *et al.* (1988, 1991)
Fischer 344 (F)	8	Post-initiation	30	5–10 mg/kg bw DMBA, p.o., killed at 77 or 133 days after carcinogen	Voluntary – wheel cage	No effect	Cohen *et al.* (1993)
Fischer 344 (F)	7	Post-initiation	28–30	50 mg/kg bw MNU, 1 x wk, 2 weeks, i.p., killed 3 months after carcinogen	Treadmill	Decrease	Thompson *et al.* (1995)

Table 47 (contd)

Organ site/ species/ strain (sex)	Age at beginning of the study (wk)	Study type	No. per group	Carcinogen exposure	Type of exercise	Results	Reference
Sprague-Dawley (F)	3	Pre-initiation	26–29	50 mg/kg bw MNU, at 50 days i.p., killed 24 weeks after carcinogen	Treadmill	Decrease	Whittal & Parkhouse (1996)
Fischer 344 (F)	7	Post-initiation	30–32	50 mg/kg bw MNU, 1 x wk, 2 weeks, i.p., killed 20.5 weeks after carcinogen	Treadmill[a]	No effect	Gillette *et al.* (1997)
Sprague-Dawley (F)	3	Pre-initiation	40	37.5 mg/kg bw MNU, at 50 days, i.p., killed 22 weeks after carcinogen	Treadmill	No effect	Whittal-Strange *et al.* (1998)
Pancreas							
Hamster							
Syrian hamster (F)	4	Pre-/post-initiation	25–28	20 mg/kg bw BOP, 1 x wk, 2 weeks, s.c., killed 44 weeks after last BOP	Voluntary – wheel cage	No effect	Kazakoff *et al.* (1996)
Liver							
Rat							
Jc1:Wistar (M)	10	Concurrent	17–19	0.0177 g/kg bw/day 3'-Me-4-DAB diet starting at 27 weeks, killed at 62 weeks of age	Voluntary – wheel cage	Decrease	Ikuyama *et al.* (1993)

AOM, azoxymethane; BOP, *N*-nitrosobis(2-oxopropyl)amine; DMBA, 7,12-dimethylbenz[*a*]anthracene; DMH, 1,2-dimethylhydrazine; i.p., intraperitoneal; i.v., intravenous; 3'-Me-4-DAB, 3'-methyl-4-dimethylaminoazobenzene; MNU, *N*-methyl-*N*-nitrosourea; p.o., orally

Voluntary activity during the post-initiation stage reduced tumour yields and extended the latency period. Cohen *et al.* (1992) reported a U-shaped relationship between cumulative distance run in an activity wheel and the magnitude of the carcinogenic response, the greatest response being observed at intermediate distances.

Whittal and Parkhouse (1996) reported the effects of exercise on mammary gland development, proliferation and MNU-induced tumorigenesis. Female Sprague-Dawley rats were divided into two groups, sedentary and exercised from 21 to 50 days of age (progressive treadmill training programme with a final workload of 18 m/min at 15% incline for 60 min per day). At 50 days of age, 24 hours after exercise, animals were given an intraperitoneal injection of MNU at 50 mg/kg bw. At the termination of the experiment at 24 weeks after carcinogen treatment, the total number of tumours was reduced by exercise (from 58 to 33 carcinomas, $p < 0.05$, 1.3 ± 0.24 tumours per animal versus 2.0 ± 3.5 in the sedentary group). The latency period was not affected and the tumour incidences were similar (68.9% and 61.5%) in sedentary and exercised rats. The results were not associated with any change in the degree of mammary gland development or proliferation status at the time of MNU administration.

Whittal-Strange *et al.* (1998) further described effects of exercise on MNU-induced mammary tumorigenesis. Female Sprague-Dawley rats, divided into two groups, sedentary and exercised from 21 to 50 days of age (progressive treadmill training programme with a final workload of 18 m/min at 15% incline for 60 min per day), were given an intraperitoneal injection of MNU at 35 mg/kg bw at 50 days of age. At the termination of the experiment 22 weeks after carcinogen treatment, the tumour incidence, multiplicity and latency did not show any difference between the groups, but the tumour growth rate and the final tumour weight were significantly higher in the exercised animals.

In BALB/c mice treated with DMBA, tumour incidence was not affected by treadmill exercise in animals fed a standard diet, but was significantly reduced in exercised mice fed a restricted or a high-fat diet (Lane *et al.*, 1991).

Pancreas

Kazakoff *et al.* (1996) determined the effects of voluntary physical activity on high-fat diet-promoted pancreatic carcinogenesis in hamsters. Groups of female Syrian hamsters were fed a high-fat diet (24.6% w/w corn oil) or low-fat diet (4.5% w/w corn oil). Each group was subdivided into an exercise and a sedentary group. All hamsters were fed their diets for four weeks, then given two injections of 20 mg/kg bw BOP with a one-week interval. Diets were continued until week 44 after the BOP treatment. No significant difference in incidence of carcinomas *in situ* or pancreatic ductal/ductular adenocarcinomas was observed between the exercise and sedentary groups.

Liver

The effects of voluntary physical activity on induction of hepatomas by 3′-methyl-4-dimethylaminoazobenzene were investigated in male Jc1:Wistar rats, divided into sedentary and exercise groups and maintained in individual cages (Ikuyama *et al.*, 1993). Food intake and wheel-running were automatically controlled in the cages of the exercise group. From 27 weeks to the termination of the study at week 62, the animals were fed the carcinogen in the diet at 0.0177 g/day/kg body weight. The incidence of hepatomas [histology not specified] was significantly lower in the exercise group (0% versus 65% in the sedentary group).

Intermediate biomarkers – weight control

Intermediate end-point biomarkers are cellular, biochemical and/or molecular determinants of the risk for subsequent development of cancer. These markers may represent intermediate stages in the development of cancer or be causally involved in the etiology of cancer, and/or reflect changes in cellular processes that occur in parallel to the initiation, promotion and/or progression stage(s) of carcinogenesis. Intermediate markers discussed in this section can be grouped under one of these categories. Some of these markers are also discussed in the section on mechanisms later in this chapter, since mechanistic studies frequently identify candidate intermediate biomarkers.

The number of animal experiments in which the effects of energy restriction on intermediate end-point biomarkers for cancer have been investigated is limited (Table 48).

Colon

The effects of 20–30% energy restriction on the rate of colonic cell proliferation, stated by the authors to be an intermediate biomarker for colon cancer risk, was investigated in male Fischer 344 rats treated with AOM as a colon-specific carcinogen (Steinbach *et al.*, 1993). Energy restriction was shown to inhibit tumour formation. Both the DNA labelling index, determined by [^{3}H]thymidine incorporation, and the number of labelled cells per crypt column were reduced by energy restriction in both carcinogen-treated and control rats in normal-appearing mucosa. The effect was seen after as little as 10 and 20 weeks of energy restriction and persisted at 34 weeks. These findings are indicative of a reduced risk for cancer. Lasko and co-workers also studied the effects of 20% energy restriction on a different intermediate biomarker for colon cancer, aberrant crypt foci (ACF), in rats treated with AOM (Lasko & Bird 1995; Lasko *et al.*, 1999). A moderate level of energy restriction (20%) reduced the total number of ACF regardless of the level of fat, but retarded the appearance of

Table 48. Modulation by energy restriction of intermediate biomarkers in animal models

Organ site/ species/strain (sex)	Magnitude of restriction	Duration of feeding	Genotoxic agent (dose and schedule)	Investigated effect	Result[a]	Reference
Colon						
Rat						
Fischer 344 (M)	20 or 30%	10, 20, 21, 34 wks	AOM, 15 mg/kg bw, 1 x wk, 2 weeks, s.c.	Colon cell proliferation ([^{3}H]thymidine incorporation)	Decreased	Steinbach *et al.* (1993)
Fischer 344 (M)	20%	Restriction delayed for 11 wks and imposed for 12 wks	AOM, 15 mg/kg bw, 1 x wk, 2 weeks, s.c.	Aberrant crypt foci	Decreased	Lasko & Bird (1995)
Fischer 344 (M)	20%	Restriction delayed for 16 wks and imposed for 6 wks	AOM, 15 mg/kg bw, 1 x wk, 3 weeks, s.c.	Aberrant crypt foci	Decreased	Lasko *et al.* (1999)
Mammary gland						
Mouse						
C3H/HeOu (F)	19%	6, 8, 10 and 12 wks	Spontaneous	EGF mRNA or protein at 12 weeks		Engelman *et al.* (1995)
				Submandibular gland	Decreased	
				Mammary gland	Decreased	
				Serum EGF protein	No change	
Pancreas						
Rat						
Lewis (M)	10–30%	16 wk	Azaserine, 30 mg/kg, once	Acidophilic pancreatic foci	Dose-dependent decrease	Roebuck *et al.* (1993)
Liver						
Mouse						
B6C3F$_1$	40%	Continuous, multiple age groups	Spontaneous model	Pi-class glutathione *S*-transferase (GST-II) hepatic foci	Decreased	Muskhelishvili *et al.* (1996)
Rat						
Fischer 344 (M)	30%	32 wks	AOM, 15 mg bw, 1 x wk, 2 weeks, s.c.	GST-P (placental form) -positive hepatic foci	Decreased	Sugie *et al.* (1993)
Fischer 344 (M)	40%	6 wks	Aflatoxin B$_1$ 0.1 mg 1,6 or 15 times, p.o.	Aflatoxin B$_1$-DNA	Decreased	Chou *et al.* (1993a)
			Benzo[a]pyrene (BP) 1 mmol/ml/kg bw, 1 or 3 times, i.p.	BP-DNA adducts	Increased	

AOM, azoxymethane; BP, benzo[*a*]pyrene; i.p., intraperitoneal; p.o., oral; s.c., subcutaneous

[a] Statistically significant, $p < 0.05$

advanced ACF only when dietary fat was low (5% w/w) but not high (23% w/w). This effect, which was consistently observed only in animals fed the low-fat diet, was seen when energy restriction was initiated either 11 or 16 weeks after AOM treatment, times at which advanced ACF were present in the colon.

Mammary gland

Insulin-like growth factor metabolism has been proposed as a candidate intermediate marker for cancer at several sites including the mammary gland. The effects of energy restriction on this intermediate end-point are considered in the section on mechanisms later in this chapter. The effect of energy restriction (19%) on the expression of epidermal growth factor (EGF, mRNA and protein levels) was investigated in the submandibular gland, mammary gland and serum (protein only) of female C3H/HeOu mice that develop mammary tumours in response to mouse mammary tumour virus (MMTV) (Engelman *et al.*, 1995). Effects were evaluated at 6, 8, 10 and 12 weeks. Levels of EGF mRNA and protein in tissue were lower in energy-restricted animals than in *ad libitum*-fed controls at the later time points, but no differences were observed in serum concentrations of EGF. The authors suggested that reduced levels of EGF in tumour tissue might contribute to the antiproliferative effects of energy restriction and reduced incidence of carcinomas in this mammary tumour model.

Pancreas

The effect of several levels of energy restriction (10, 15, 20 and 30%) on azaserine-induced pancreatic carcinogenesis in the rat has been studied (Roebuck *et al.*, 1993). A progressive reduction in the occurrence of acidophilic pancreatic foci, an intermediate biomarker for pancreatic carcinomas, was observed with increasing degree of energy restriction.

Liver

Energy restriction has been reported to inhibit the occurrence of glutathione-*S*-transferase (GST)-positive hepatic foci, an intermediate biomarker for the development of hepatocellular carcinomas. Muskhelishvili *et al.* (1996) studied the effects of dietary restriction on the spontaneous occurrence of GST-II (pi-class)-positive foci in male B6C3F1 mice that are tumour-prone. [The Working Group noted that GST-pi-positive foci have not been shown to be precursor lesions for hepatocellular carcinoma in mice.] Dietary restriction diminished GST-II expression with a marked reduction in the incidence of liver tumours. Sugie *et al.* (1993) examined the effect of energy restriction (30%) on the induction of GST-P (placental form)-positive foci in rat liver following administration of AOM, which is usually considered a colon-specific carcinogen. The density and size of GST-P-positive foci were significantly lower in AOM-treated, energy-restricted animals, but the incidence of foci was unaffected in AOM-treated energy-restricted rats relative to the AOM-treated control group. Energy restriction (40%) has been reported to modulate the formation of carcinogen–DNA adducts in the liver. Whereas the formation of aflatoxin B_1–DNA adducts was reduced in parallel with a reduction in CYP2C11, which is involved in aflatoxin B_1 activation, BP–DNA adducts were increased (Chou *et al.*, 1993a). The increase correlated with an increase in BP-metabolizing enzymes. The implications of these findings are discussed in the section on mechanisms later in this chapter.

Oncogene expression

Effects of energy restriction (30–40%) on oncogene expression have been reported (Nakamura *et al.*, 1989; Baik *et al.*, 1992; Himeno *et al.*, 1992; Fernandes *et al.*, 1995). Three of these experiments were not designed specifically to investigate the cancer-preventive activity of energy restriction and in one (Fernandes *et al.*, 1995), oncogene expression was studied in tumours that occurred despite energy restriction. Therefore, the results must be interpreted with caution, since the changes in oncogene expression observed may have little relevance to cancer prevention *per se*. Nonetheless, the data suggest that energy restriction leads to down-regulation of expression of *c*-Ha-*ras* and *c-fos* mRNA in mammary tissue (30% restriction) but not in liver (Baik *et al.*, 1992). Hepatic *c-myc* proto-oncogene expression was reduced in chronically restricted (40%) C57B16 × C3HF1 hybrid mice (Nakamura *et al.*, 1989). The authors speculated that c-*myc* expression may be linked to metabolic activity and to lower rates of hepatic cell proliferation in energy-restricted mice. Oncogene expression during liver regeneration was also studied (Himeno *et al.*, 1992). Energy restriction (40%) preserved inducible cellular responses in response to partial hepatectomy, i.e., [^{3}H]thymidine incorporation, but lowered the elevated oncogene expression observed in response to partial hepatectomy relative to the response observed in *ad libitum*-fed controls.

Fernandes *et al.* (1995) studied the correlation of oncogene and tumour-suppressor gene changes with the cancer-preventive activity of energy restriction in an MMTV/v-Ha-*ras* model. In mammary tumours that occurred despite 40% energy restriction, the restriction led to lower expression and mRNA levels of v-Ha-*ras* and *neu*, and increased wild-type *p53* expression. The authors speculated that these changes reflected molecular alterations involved in the inhibition of mammary carcinoma induction in this model.

Intermediate biomarkers – physical activity

Few animal experiments have investigated the effects of physical activity on intermediate end-point biomarkers for cancer (Table 49).

Table 49. Modulation by physical activity of intermediate biomarkers in animal models

Organ site/ species/strain (sex)	Type of physical activity	Duration and intensity of physical activity	Genotoxic agent (dose and schedule)	Investigated effect	Result	Reference
Liver						
Rat						
Fischer 344 (M)	Wheel-running for 38 weeks, initiated 4 days after last AOM injection	Voluntary Peak: wk 6 Distance run diminished over time	AOM, 15 mg/kg bw, 1 x wk, 2 weeks, s.c.	GST-P hepatic foci Density Size Incidence	 Decreased* Decreased* No effect	Sugie *et al.* (1992)
Pancreas						
Rat						
Lewis (M) Fischer 344 (F)	Wheel-running for up to 18 weeks, started after azaserine injection	Voluntary Peak: 6–12 week depending on gender Distance run diminished over time	Azaserine males: 30 mg/kg bw once, i.p. Females: 30 mg/kg bw x 3 times, i.p.	Volume% 4 months after initiation Acidophilic acinar-cell foci Basophilic acinar-cell foci Labelling index: [^{3}H]thymidine incorporation	 Reduced in males* and females – NS No effect in males; reduced in females* Reduced – NS	Roebuck *et al.* (1990)
Lewis (M)	Treadmill running	Progressive training programme, final work-load of 16 m/min, 7.5° incline, 5 days/week, 7 wk training, 18 wk exercise	Azaserine, 30 mg/kg bw once, i.p.	Acidophilic pancreatic foci: Volume%	Increased – NS	Craven-Giles *et al.* (1994)
Mammary gland						
Rat						
Sprague-Dawley (F)	Treadmill running with air jet reinforcement	Progressive training programme: final workload of 18 m/min on a 15% incline for 60 min, 5 days per week from 21 to 50 days of age	MNU, 50 mg/kg bw, i.p. at 50 days of age	Continuous labelling with BrdU for 4 days at 46 days of age (mammary gland) Developmental score for the mammary gland	No difference No difference	Whittal & Parkhouse (1996)

*Reported effect was statistically significant, $p < 0.05$; NS, not statistically significant
AOM, azoxymethane; BrdU, bromodeoxyuridine; GST, glutathione-*S*-transferase; i.p., intraperitoneal; MNU, *N*-methyl-*N*-nitrosourea; NS, not significant; s.c., subcutaneous

Liver

The effect of voluntary physical activity (wheel-running) on carcinogen-induced GST-P (placental form)-positive (enzyme-altered) foci in liver was studied by Sugie *et al.* (1992). Voluntary access to an activity wheel was initiated following carcinogen administration (AOM, subcutaneous injection, 5 mg/kg bw × 2). The density and size of GST-P hepatic foci were reduced significantly in active versus sedentary animals; the incidence of altered foci was unaffected. These results were interpreted by the authors to indicate that activity may inhibit chemically induced hepatocarcinogenesis. [The Working Group noted that activity was not uniform throughout the experiment, peaking at week 6 after carcinogen treatment and declining thereafter].

Pancreas

Roebuck *et al.* (1990) studied the effect of wheel-running on intermediate biomarkers for pancreatic cancer, namely formation of acidophilic and basophilic pancreatic foci and [^{3}H]thymidine incorporation as a measure of cell proliferation within foci. Variable effects on these markers in response to exercise were observed and frequently differences between the active and sedentary groups did not reach the level of statistical significance. The authors concluded that male and female rats with free access to running wheels had significantly smaller foci and lower rates of thymidine incorporation into foci four months after initiation. These effects occurred late in the post-initiation phase and were not directly related to the extent of running activity early in the post-initiation phase. [The Working Group noted the reduction of running activity over time during this study. Also, the responses were not consistent with gender, and/or were not statistically significant.]

In a second series of studies, Craven-Giles *et al.* (1994) investigated modulation of pancreatic foci by treadmill running. Male Lewis rats were treated with azaserine at two weeks of age and weaned to experimental protocols at three weeks of age. Two experiments were undertaken: treadmill exercise began at six weeks of age (Experiment 1) or at 13 weeks of age (Experiment 2). Rats were exercised for 15–20 min/day and for three to five days per week. Treadmill speed and angle of incline were adjusted to afford a range of exercise intensities. The development of pancreatic acinar foci was evaluated by quantitative stereological analysis using light microscopy. In Experiment 1, exercise resulted in a known paradoxical reduction in food intake by about 15% of the intake of the sedentary group fed *ad libitum*. The burden of azaserine-induced foci was decreased by approximately 37%, and this was attributed to the known effects of reduced energy intake in these young, rapidly growing rats. In Experiment 2, the higher-intensity treadmill exercise group had an increased focal burden compared with their sedentary pair-fed controls despite a reduction in food intake and body fat stores. These experiments demonstrate that exercise may reduce or enhance the occurrence of acinar foci, depending upon the intensity of the exercise and the stage in the life cycle of the animal at which exercise is imposed. This enhancement of focal burden represents a potential adverse effect of physical activity, as noted in Chapter 7.

Mammary gland

Whittal and Parkhouse (1996) studied the effects of treadmill exercise for four weeks on both the developmental stage and level of proliferation in the mammary gland at the time of carcinogenic initiation. Both factors have been reported to be associated with risk for carcinogenic transformation. Neither parameter was affected by treadmill exercise. Cancer end-points were also assessed in additional groups of animals that received identical treatment. Exercise reduced the multiplicity of mammary carcinomas but not their incidence (see above).

Enzymes

Since activities of phase II enzymes have been inversely associated with cancer risk, their activities may have value as intermediate biomarkers. Duncan *et al.* (1997) examined whether a progressive treadmill training programme for seven weeks would modulate constitutive levels of phase II or antioxidant enzymes in liver or lung. While response to exercise varied with the tissue and the enzymes assayed, in general the activities of superoxide dismutase, catalase, UDP-glucuronosyl transferase and GST were increased by exercise. The authors interpreted their data as being consistent with the hypothesis that exercise would prevent liver and lung cancer. [The Working Group noted that no data were presented to show that the exercise training programme investigated would actually affect the occurrence of either liver or lung cancer in an animal model system.]

Mechanisms of cancer prevention

The observations that weight, weight change and physical activity are associated with cancer occurrence are supported by evidence of biological plausibility for these associations. In Chapter 3, the relationships between physical activity and BMI, and in particular the possible contribution of physical activity to preventing or reducing weight excess, have been discussed. As reviewed in Chapter 4, body mass, fat distribution and physical activity can have profound effects on many physiological factors that may be important in cancer etiology. These reviews show that the effects of physical activity on metabolic factors are mediated only in part by improved weight control.

This section reviews the human and animal evidence for the role of physiological and metabolic factors in cancer development. These factors include mainly endogenous hormones, particularly those hormones (sex steroids, insulin, insulin-like growth factor-I (IGF-I)) for which epidemiological studies have shown at least some direct or indirect evidence for involvement in cancer development. Other mechanisms briefly discussed relate to gastro-oesophageal reflux in relation to oesophageal adenomas, intestinal transit time and bile acid metabolism in relation to colorectal cancer, and immune function.

Human studies

Endogenous hormones and cancer risk

Sex steroids

One major class of mechanisms that may form a physiological and causal link between energy balance and cancer risk comprises alterations of endogenous hormone metabolism. Much attention has been focused on endogenous sex steroids as possible determinants of tumours of, in particular, the breast, endometrium, ovary and prostate. The role of sex steroids in regulating the balance between cellular differentiation, mitosis and apoptosis is well established, and it has been postulated that alterations in the endocrine environment may favour the selective growth of preneoplastic and neoplastic cells (Henderson *et al.*, 1988; Dickson *et al.*, 1990).

The risks of cancers of the breast, endometrium and ovary are related to factors such as early menarche, late menopause, age at first full-term pregnancy and parity. With increasing age, age-specific incidence rates of cancers of the breast and endometrium rise faster before than after menopause, when the ovaries stop producing estrogens and progesterone. Together, these observations provide indirect evidence for the role of ovarian activity and sex steroids as modulators of the risk of these cancers. This hypothesis is supported by observations that risk of cancers of the breast, endometrium and ovary can be increased or decreased by use of exogenous estrogens or progestogens (or combinations of these) for contraception or postmenopausal therapy.

The predominant theory relating the risk of endometrial cancer to endogenous sex steroids is the 'unopposed estrogen' hypothesis. This proposes that risk is increased among women who have normal or elevated plasma levels of bioavailable estrogens but low levels of progesterone, so that biological effects of estrogens are insufficiently counterbalanced by those of progesterone (Key & Pike, 1988; Grady & Ernster, 1996). This hypothesis is supported by observations that use of exogenous hormones for contraception or postmenopausal replacement therapy is associated with an increase in endometrial cancer risk when the hormone preparations contain only estrogens, whereas combinations of estrogens plus progestogens confer a relative protection (van Leeuwen & Rookus, 1989; Grady & Ernster, 1996; IARC, 1999; Weiderpass *et al.*, 1999a, b). Studies *in vitro* have shown that estrogens stimulate the proliferation of normal endometrial tissue as well as of endometrial tumour cells, and that at least part of this effect may be mediated by an increase in local IGF-I concentrations (Rutanen, 1998). The opposing effects of progestogens, on the other hand, appear to be due largely to progesterone's capacity to increase levels of IGF-binding protein-1 (IGFBP-1) in endometrium (Rutanen, 1998).

Case–control studies have shown an increase in endometrial cancer risk in women who have low levels of plasma sex-hormone-binding globulin (SHBG), elevated levels of androgens (Δ4-androstenedione, testosterone) and, particularly after menopause, elevated levels of total and bioavailable estrogens (estradiol, estrone) (Austin *et al.*, 1991; Möllerström *et al.*, 1993; Nyholm *et al.*, 1993; Grady & Ernster, 1996; Potischman *et al.*, 1996). Before menopause, endometrial cancer risk may be related more to the lack of progesterone than to an excess of total or bioavailable estrogens (Key & Pike, 1988; Grady & Ernster, 1996; Potischman *et al.*, 1996). Ovarian hyperandrogenism appears to be an important risk factor for endometrial cancer in premenopausal women, as suggested by a large number of case reports of polycystic ovary syndrome (PCOS) in young cancer patients (Grady & Ernster, 1996) and by case–control (Dahlgren *et al.*, 1991; Shu *et al.*, 1991; Niwa *et al.*, 2000) and cohort (Coulam *et al.*, 1983) studies showing an increased risk of endometrial cancer among women who have PCOS. PCOS is generally associated with chronic anovulation, and hence with low production of progesterone.

Taken together, these observations, along with those discussed above on relationships with insulin and IGFBP-1, strongly support the hypothesis that, in premenopausal women, obesity and chronic hyperinsulinaemia may increase endometrial cancer risk by inducing ovarian hyperandrogenism, chronic anovulation and insufficient ovarian progesterone production. The lack of progesterone plus elevated plasma insulin level causes a drop in endometrial IGFBP-1 levels, while normal or moderately elevated estrogen levels increase local IGF-I concentrations. The ensuing increase in local IGF-I activity, plus other effects of estrogens and progesterone on endometrial tissue, may favour tumour development. After meno-pause, when progesterone production has ceased altogether, chronic hyperinsulinaemia may also increase endometrial cancer risk because of elevated insulin levels, decreased endometrial IGFBP-1 concentrations and increases in total and bioavailable plasma estrogen concentrations.

With respect to breast cancer, there is strong evidence that risk is increased in women with elevated plasma and tissue levels of estrogens ('estrogen excess' hypothesis) (Bernstein & Ross, 1993). This is supported by observations from prospective cohort studies showing increased breast cancer incidence in postmenopausal women who have low levels of SHBG and elevated levels of total and bioavailable androgens and estrogens (Thomas *et al.*, 1997; Hankinson *et al.*, 1998a; Kabuto *et al.*, 2000). Since obesity and the associated chronic hyperinsulinaemia decrease levels of SHBG and, in postmenopausal women, increase levels of androgens plus estrogens, the estrogen excess theory can also explain the increased breast cancer risk in postmenopausal women who are overweight or obese.

A second, more extensive theory is that, beyond the effect of exposure to estrogens alone, breast cancer risk is increased further when women are exposed to a combination of estrogens and progestogens ('estrogen-plus-progestogen' hypothesis). This hypothesis is supported by recent results showing that women using combined estrogen-plus-progestogen preparations for postmenopausal replacement therapy have a greater increase in risk than women using preparations containing only estrogens (IARC, 1999; Magnusson *et al.*, 1999; Ross *et al.*, 2000b; Schairer *et al.*, 2000). In addition, since in premenopausal women obesity may lead to chronic anovulation and decreased progesterone levels (especially in women with a predisposition towards ovarian hyperandrogenism), this second theory could also explain why on average obesity appears to be inversely related to breast cancer risk in premenopausal women.

Reducing cumulative exposure to ovarian hormones by delaying menarche and/or by reducing the number of ovulatory cycles (Bernstein *et al.*, 1987; Keizer & Rogol, 1990; Loucks, 1990; Meyer *et al.*, 1990; Moisan *et al.*, 1991; Greene, 1993; Merzenich *et al.*, 1993; Petridou *et al.*, 1996) may decrease the risk of cancers of breast. Anovulatory cycles are associated with marked changes in endogenous estrogens and progesterone, which may lower risk for breast cancer (Pike *et al.*, 1983).

Further theories propose that specific metabolites of estradiol and estrone that may be formed locally within breast tissue increase risk. One such theory is that an increased ratio of 16-hydroxy- to 2-hydroxy-estrogens increases risk (Bradlow *et al.*, 1986). This hypothesis is supported by some recent findings (Kabat *et al.*, 1997; Meilahn *et al.*, 1998; Muti *et al.*, 2000) but not by others (Ursin *et al.*, 1999). The ratio of 16-hydroxy- to 2-hydroxy-metabolites has been found to be increased in obese subjects and low in women with anorexia nervosa (Fishman *et al.*, 1975). Exercise, on the other hand, has been reported to reduce 2-hydroxy-estrogen levels (de Crée *et al.*, 1997c).

The etiopathogenesis of ovarian cancer is still poorly understood. One hypothesis is that many years of uninterrupted ovulatory cycles increase risk by enhancing entrapment of ovarian epithelium in inclusion cysts and/or by repeated damage of the surface epithelium during ovulation ('incessant ovulation' hypothesis) (Fathalla, 1971; Cramer & Welch 1983; Cramer *et al.*, 1983). This hypothesis is based almost entirely on indirect epidemiological evidence, which shows that high parity and regular use of oral contraceptives are protective factors. A second complementary hypothesis, based largely on evidence from animal experiments, is that tumour development is promoted by elevated ovarian exposure to luteinizing hormone (LH) ('gonadotropin' hypothesis) (Weiss *et al.*, 1996; Blaakaer, 1997). Both the incessant ovulation hypothesis and the gonadotropin hypothesis find some indirect support in observations that oral contraceptives decrease ovarian cancer risk (Whittemore, 1993; Weiss *et al.*, 1996; Blaakaer, 1997). Exercise might prevent ovarian cancer by reducing the number of lifetime ovulatory cycles, since it has been shown to be associated with delayed menarche, amenorrhoea and anovulatory cycles (Frisch *et al.*, 1981; Russell *et al.*, 1984; Bernstein *et al.*, 1987; Moisan *et al.*, 1991; Whittemore, 1993). However, regular strenuous exercise seems to be needed to produce these effects.

Elevated pituitary secretion of LH is also a characteristic of women who have PCOS, and in one prospective study, PCOS was found to be associated with increased ovarian cancer risk (Schildkraut *et al.*, 1996). In another prospective study, 13 premenopausal women and 18 postmenopausal women who eventually developed ovarian cancer had higher prediagnostic serum levels of Δ4-androstenedione than age-matched control subjects from the same cohort (Helzlsouer *et al.*, 1995). These and other observations led to an extension of the gonadotropin hypothesis, which proposes that ovarian tumour development may be enhanced by excess ovarian production of androgens (Risch, 1998). Ovarian hyperandrogenism might also provide a link between a positive energy balance and ovarian cancer risk, since in women with a predisposition towards ovarian hyperandrogenism, adiposity and chronic hyperinsulinaemia might exacerbate the ovarian androgen excess. However, in hyperandrogenic women, obesity and chronic hyperinsulinaemia also cause more frequent anovulation; thus, following the incessant ovulation hypothesis, one could equally well expect that obesity or chronic hyperinsulinaemia would reduce risk. There is currently insufficient evidence to evaluate whether only milder forms of ovarian androgen excess, without chronic anovulation, constitute a risk factor for ovarian cancer. As reviewed

earlier in this chapter, there is also insufficient evidence to conclude whether or not ovarian cancer risk is related to obesity.

Overall, the observation that, depending on cancer site and type of preparation used, exogenous hormones can either increase or decrease risk of cancers of the breast, endometrium or ovary shows that hormones can affect the development of these cancers at a relatively late stage during adulthood. Combined with the fact that weight loss can favourably change endogenous hormone profiles in initially obese women, this strongly suggests that weight loss may also have cancer-preventive effects even if initiated relatively late in life.

In men, a strong indication for the implication of sex steroids in prostate tumour progression is that surgical or medical castration can dramatically improve the clinical course of prostate cancer patients. Extensive animal research has also indicated the involvement of endogenous sex steroids in the development of such tumours. Nevertheless, the etiopathogenesis of prostate cancer remains poorly understood, although a role for androgens and/or estrogens appears likely (Bosland, 2000; Kaaks *et al.*, 2000a). The predominant hypothesis is that risk is increased in men who have elevated intraprostatic concentrations of dihydrotestosterone (DHT). DHT is formed from testosterone within the prostate by the enzyme 5-reductase type II (SRD5A). Interindividual differences in SRD5A activity, due to polymorphic variations in the SRD5A gene (Ross *et al.*, 1998) or to differences in physiological regulation, may cause variations in amounts of DHT formed and thus in prostate cancer risk (Bosland, 2000).

Another possible determinant of levels of intraprostatic DHT formation is the level of bioavailable testosterone in the circulation. One large prospective cohort study found a strong trend of increasing prostate cancer risk with increasing levels of plasma testosterone adjusting for SHBG, whereas risk was inversely related to levels of SHBG after adjustment for testosterone (Gann *et al.*, 1996). However, these results have not been confirmed by other prospective cohort studies (Bosland, 2000; Kaaks *et al.*, 2000a) and in a formal meta-analysis of all reported prospective studies, risk was found to be unassociated with levels of either total or bioavailable testosterone (Eaton *et al.*, 1999). It remains possible, however, that difficulties in accurately measuring levels of bioavailable hormones obscured the presence of a relatively weak association with prostate cancer risk (Kaaks *et al.*, 2000a). Besides androgens, estrogens have also been proposed to either enhance or inhibit prostate cancer development (Farnsworth, 1996; Chang & Prins, 1999; Bosland, 2000), but the lack of any association of prostate cancer risk with plasma estrogen levels supports neither of these hypotheses (Eaton *et al.*, 1999; Bosland, 2000).

In summary, it remains unclear whether variations in bioavailable androgens (and possibly other sex steroids) are entirely unrelated to prostate cancer risk, or whether weak associations exist that may have been obscured by, for example, inaccuracies in hormone measurements. Even if prostate cancer risk were related to bioavailable androgen levels, however, the lack of any direct relationship of plasma bioavailable androgens with anthropometric measures of adiposity or physical activity levels would be consistent with the absence of an association between either obesity or physical activity and prostate cancer risk, as reviewed earlier in this chapter.

There is indirect evidence that sex steroids may also influence the development of colorectal cancer. Incidence rates are higher in men than in women, especially for the more distal colon, and use of postmenopausal estrogen supplements by women is associated with decreased risk of colorectal cancer (Calle *et al.*, 1995; Kampman *et al.*, 1997; Crandall, 1999) and colorectal adenomas (Potter *et al.*, 1996). The mechanisms for this association are not well understood, but estrogen receptors are expressed by colonocytes. It has been proposed that the weaker association between BMI and colon cancer for women than for men might also be related to differences in estrogen metabolism between men and women. Women who are overweight after the menopause have higher circulating estrogen levels due to the conversion of estrogen precursors to estrogen in adipose tissues. If estrogens do, indeed, reduce colorectal cancer risk, this could account for the gender difference in the strength of the association with obesity. A counterargument, however, is that obesity is related to increased plasma estrogen levels also in men and that plasma estrogen concentrations in men and postmenopausal women are approximately identical.

Insulin, IGFBP-1 and IGFBP-2

Insulin, IGF-I and IGF-binding proteins are receiving increasing attention from molecular biologists, pathologists and epidemiologists (Giovannucci, 1995, 1999; Kaaks *et al.*, 2000a; Khandwala *et al.*, 2000; Pollak, 2000; Kaaks & Lukanova, 2001). Insulin and IGF-I stimulate the proliferation (mitosis) and inhibit the programmed death (apoptosis) of both normal and neoplastic cells of many types (Werner & LeRoith, 1996; Khandwala *et al.*, 2000). Both hormones also have effects on cellular (de-) differentiation (Benito *et al.*, 1996; Stewart & Rotwein, 1996; Werner & LeRoith, 1996; Yu & Berkel, 1999; Khandwala *et al.*, 2000) and angiogenesis (Grant *et al.*, 1993; Kluge *et al.*, 1995) and have been reported to favour neoplastic transformation. Insulin and IGF-I exert these trophic effects on a wide variety of tissue types including cells from the breast (Foekens *et al.*, 1989; Yee *et al.*, 1989), endometrium (Rutanen, 1998; Wang & Chard, 1999), ovary (Wang & Chard, 1999;

Poretsky *et al.*, 1999), colon (Singh & Rubin, 1993; Kim, 1998; Burroughs *et al.*, 1999; Rosen, 1999), prostate (Pollak *et al.*, 1998; Wong & Wang, 2000) and kidney (Hammerman, 1999). In some tissue types (e.g., breast, endometrium and prostate), these effects of IGF-I have been proven to be synergistic with those of other growth factors and steroids (Dickson *et al.*, 1990; Westley & May 1994; Westley *et al.*, 1998; Yee & Lee, 2000).

As reviewed in the first part of this chapter, epidemiological studies have shown that excess body weight and obesity are positively associated with risk of cancers of the endometrium (in pre- and postmenopausal women), breast (only for tumours diagnosed several years after menopause) colon, oesophagus (adenocarcinoma) and kidney (renal cell cancer). The risk of breast cancer before menopause, by contrast, appears to be slightly decreased by obesity. As discussed in Chapter 4, one major metabolic consequence of obesity is insulin resistance, an increase in fasting plasma glucose and insulin concentrations, and decreases in IGFBP-1 and IGFBP-2 levels (down-regulated by insulin). The relationship of colon cancer risk with obesity, as well as with other dietary and lifestyle factors thought to be related to insulin resistance (e.g., low intake of n–3 polyunsaturated fatty acids, dietary fibre and fruits and vegetables; high intake of sucrose and other carbohydrates of high glycaemic index; low levels of physical activity), led to the hypothesis that chronically elevated insulin levels may be a direct risk factor for colon cancer (McKeown-Eyssen, 1994; Giovannucci, 1995; Kim, 1998). Similar hypotheses have been formulated for cancers of the breast (Kaaks, 1996; Stoll, 1999), pancreas (Weiderpass *et al.*, 1998) and endometrium (Rutanen *et al.*, 1993; Rutanen, 1998). The tumour-enhancing effects might be due either to insulin itself or to an increase in IGF-I bioactivity that may result from insulin-induced reductions in IGFBP-1 and -2. One physiological mechanism through which regular physical exercise may decrease cancer risk, and actually oppose the metabolic effects of obesity, is reduced insulin resistance, chronic hyperinsulinaemia and increased IGFBP-1 (see Chapter 4).

The hypothesis that chronic hyperinsulinaemia may enhance the development of these various forms of cancer finds indirect support in observations that the risk of cancers of the colon (or colorectum) (McKeown-Eyssen, 1994; Giovannucci, 1995; La Vecchia *et al.*, 1997b; LeMarchand *et al.*, 1997; Weiderpass *et al.*, 1997; Will *et al.*, 1998; Hu *et al.*, 1999a), endometrium (Adami *et al.*, 1991; Moseson *et al.*, 1993; O'Mara *et al.*, 1985; Parazzini *et al.*, 1999; Niwa *et al.*, 2000; Weiderpass *et al.*, 2000), pancreas (Everhart & Wright, 1995; Wideroff *et al.*, 1997; Calle *et al.*, 1998b; Weiderpass *et al.*, 1998; Silverman *et al.*, 1999) and kidney (O'Mara *et al.*, 1985; Coughlin *et al.*, 1997; Wideroff *et al.*, 1997; Lindblad *et al.*, 1999) is increased in diabetics. A limitation of many of these studies is that they lacked detail as to whether diabetes was of early onset (type I) or adult onset (type II) and whether or not the subjects depended on insulin injections. However, within the general population, the majority (>80%) of diabetes is of adult onset and non-insulin-dependent. This type of diabetes is usually associated with pancreatic hypersecretion and increased plasma levels of insulin, even though the high insulin levels are insufficient to maintain normal plasma glucose levels because of insulin resistance. Case–control and prospective cohort studies have shown no consistent evidence for any association of diabetes with risk of breast cancer (Kaaks, 1996) or prostate cancer (Kaaks *et al.*, 2000a).

In addition to studies relating cancer risk to diabetes, a few recent studies have directly related cancer risk to plasma levels of insulin, C-peptide (a marker of pancreatic insulin secretion), or IGFBPs -1 and -2.

A recent cohort study showed an increase in colorectal cancer risk in men and women who had elevated fasting plasma glucose levels and higher plasma levels of glucose and insulin two hours after a standard dose of oral glucose (Schoen *et al.*, 1999). The association of colorectal cancer risk with fasting glucose levels confirmed results from some previous studies, reviewed by McKeown-Eyssen (1994) and by Giovannucci (1995). Another prospective study, in New York women, showed an approximately fourfold increase in colorectal cancer risk between subjects in the highest and lowest quartiles of (non-fasting) serum C-peptide levels (Kaaks *et al.*, 2000b). The association with C-peptide remained unaltered after adjustment for BMI. Furthermore, colorectal cancer risk was inversely associated with levels of IGFBP-1 and IGFBP-2.

For endometrial cancer, one large case–control study showed an increase in risk in postmenopausal women with elevated serum levels of C-peptide (Troisi *et al.*, 1997), which did not however persist after adjustment for BMI. The effect of hyperinsulinaemia on endometrial cancer risk may be mediated by a decrease in IGFBP-1, and hence an increase in IGF-I bioactivity. In endometrial tissue, IGFBP-1 is the most abundantly expressed IGF-binding protein and strongly inhibits the mitogenic action of IGF-I (Rutanen, 1998). A small study of 23 endometrial cancer patients and 27 healthy control women in Japan found lower IGFBP-I levels in the cases (Ayabe *et al.*, 1997) Another small study in Finland also showed higher fasting plasma insulin levels and lower expression of the *IGFBP-1* gene in endometrial tissue samples from endometrial cancer patients than in those from healthy controls (Rutanen *et al.*, 1994).

Two case–control studies have shown an association of both premeno-

pausal (Bruning *et al.*, 1992b; Del Giudice *et al.*, 1998) and postmenopausal (Bruning *et al.*, 1992) breast cancer with measurements of insulin or C-peptide, but this was not confirmed in a prospective study with measurements of (non-fasting) C-peptide (Toniolo *et al.*, 2000).

As reviewed in the first part of this chapter, prostate cancer risk appears to be independent of BMI, and there is also no clear evidence that a more central body fat distribution is a risk factor. These conclusions seem to be confirmed by the findings of one prospective cohort study, in which prostate cancer risk showed no clear relationship with plasma levels of (fasting) insulin, IGFBP-1, and IGFBP-2—peptides that are usually correlated with indices of adiposity (Stattin *et al.*, 2000).

For pancreas cancer, no studies have examined associations with plasma insulin or C-peptide. However, one recent prospective study showed an increase in risk of pancreas cancer in men and women who had elevated plasma glucose levels two hours after a standard oral glucose dose (Gapstur *et al.*, 2000). Elevated plasma glucose levels are indicative of insulin resistance and hence of chronically elevated pancreatic insulin production (DeFronzo, 1988).

For lung cancer, one prospective cohort study found a borderline significant association of risk with serum insulin concentration, which persisted after adjustment for BMI and for current and previous smoking (Lukanova *et al.*, 2001).

IGF-I and IGFBP-3

As reviewed in Chapter 4, growth hormone (GH) provides the key stimulus for the synthesis of IGF-I and IGFBP-3, and absolute levels of IGF-I and IGFBP-3 in the circulation are regulated largely along the GH/IGF-I axis. However, dietary intake and body reserves of energy and protein (essential amino acids) modulate these stimulatory effects of GH on the synthesis of IGF-I and IGFBP-3. Chronic energy restriction strongly reduces circulating IGF-I and IGFBP-3 levels. Paradoxically, however, obese subjects also have mildly reduced absolute IGF-I concentrations, compared with well nourished but non-obese subjects. Possible mechanisms of these paradoxical observations are discussed briefly in Chapter 4. Taken together, the data suggest that, within the low range of 18 to about 24 kg/m^2, BMI may be positively associated with IGF-I concentrations, whereas BMI values above 25 kg/m^2 may be inversely related, but this still requires confirmation.

Two case–control studies (Peyrat *et al.*, 1993; Bruning *et al.*, 1995) and two prospective cohort studies (Hankinson *et al.*, 1998b; Toniolo *et al.*, 2000) have shown an increased risk of premenopausal breast cancer in women with elevated levels of IGF-I in plasma or serum, but no association of IGF-I with postmenopausal breast cancer. A possible explanation for these findings is that IGF-I enhances breast tumour development only in the presence of, and in interaction with, elevated concentrations of estrogens. In several of these studies, the association of IGF-I with risk was stronger after adjustment for levels of IGFBP-3 (Hankinson *et al.*, 1998b) or when IGF-I levels were expressed as molar ratios to IGFBP-3 (Bruning *et al.*, 1995). Two other case–control studies, however, did not show any association between IGF-I and pre- or postmenopausal breast cancer risk (Del Giudice *et al.*, 1998; Ng *et al.*, 1998).

For colorectal cancer, three prospective cohort studies showed very small, statistically non-significant increases in risk with increasing absolute levels of IGF-I (Ma *et al.*, 1999; Giovannucci *et al.*, 2000; Kaaks *et al.*, 2000b). However, in two of these studies, the association of colorectal cancer risk with IGF-I levels became stronger, and statistically significant, after adjustment for levels of IGFBP-3 (Ma *et al.*, 1999; Giovannucci *et al.*, 2000). Furthermore, in two case–control studies, colorectal cancer risk also related directly to levels of IGF-I (Manousos *et al.*, 1999; Renehan *et al.*, 2000a) and inversely to IGFBP-3 (Manousos *et al.*, 1999). The prevalence of colorectal adenomas has long been known to be higher in patients with acromegaly, a pathology due to GH excess and associated with elevated IGF-I levels (Giovannucci, 1995). Furthermore, in one case–control study (Giovannucci *et al.*, 2000), but not another (Renehan *et al.*, 2000b), the presence of large, but not small, colorectal adenomas was found to be associated with more elevated IGF-I levels, compared with adenoma-free controls. Taken together, these observations suggest that elevated IGF-I levels may favour the progression of small to large adenomas, and possibly to carcinomas.

With regard to prostate cancer, two case–control (Mantzoros *et al.*, 1997; Wolk *et al.*, 1998) and three prospective cohort (Chan *et al.*, 1998; Harman *et al.*, 2000; Stattin *et al.*, 2000) studies have all shown an increase in prostate cancer risk in men with elevated absolute levels of IGF-I and one found an increase with elevated levels of IGF-I for given levels of IGFBP-3 (Chan *et al.*, 1998).

One case–control study showed an increase in lung cancer risk in subjects with elevated levels of IGF-I (Yu *et al.*, 1999). This association became more pronounced after adjustment for IGFBP-3 level, and after adjustment for IGF-I, risk was inversely related to IGFBP-3 levels. This study also showed a synergism between elevated IGF-I and measures of mutagen sensitivity, assessed by quantitating bleomycin- and benzo[*a*]-pyrene-induced chromatid breaks in peripheral blood lymphocyte cultures (Wu *et al.*, 2000). Another study, however, showed significantly lower IGF-I levels in lung cancer cases than in controls (Lee *et al.*, 1999b). One prospective cohort study showed no

significant association of lung cancer risk with circulating IGF-I or IGFBP-3 (Lukanova *et al.*, 2001).

Overall, these epidemiological studies show associations of risk of various forms of cancer with elevated levels of IGF-I, either as absolute concentrations or relative to levels of IGFBP-3. The increased strength of these associations, in some studies, after adjustment for IGFBP-3 may reflect increased bioavailability or bioactivity of IGF-I when IGFBP-3 levels are low. Irrespective of whether risk is associated with total IGF-I, with IGF-I adjusted for IGFBP-3, or both, these observations suggest a possible relationship of cancer risk with elevated pituitary GH secretion. Conditions of elevated GH levels, such as during the pubertal growth spurt or, at extreme levels, in acromegaly, are associated with increased levels not only of absolute IGF-I, but also of the IGF-I/IGFBP-3 ratio (Juul *et al.*, 1994; Jasper *et al.*, 1999). As discussed above, however, the relationships of absolute IGF-I levels or of IGF-I relative to IGFBP-3 with BMI are not straightforward. Further studies are required to elucidate the degree to which body fat stores and/or physical (in)activity may result in the relative increase in IGF-I (or IGF-I relative to IGFBP-3) observed in subjects who subsequently develop cancer.

It is unclear why hyperinsulinaemia and related decreases in IGFBP-1 and IGFBP-2 appear to increase the risk of some forms of cancer (e.g., colon, endometrium) but not of others (e.g., prostate cancer), for which risk is unrelated to obesity. One possible explanation for these contrasting observations is that, depending on tissue type, a decrease in IGFBP-1 or IGFBP-2 does not have the same effect on overall IGF-I bioactivity, cell proliferation and apoptosis. Paradoxically, however, those forms of cancer (e.g., of the prostate, or of the breast in premenopausal women) do show an association with absolute plasma IGF-I concentrations, or with levels of IGF-I relative to IGFBP-3. As mentioned in Chapter 4, the relationships between between circulating levels of IGF-I and IGFBPs and the concentrations of these peptides in different types of tissue remain unclear, and it is also not fully understood which specific effects each of the IGFBPs may have, in combination with IGF-I, on cellular growth, differentiation and apoptosis.

Other hormones, growth factors and non-hormonal factors

Several studies have examined the association of leptin, a hormone that reflects total fat mass, with cancer risk. Premenopausal breast cancer patients were found to have a non-significantly lower level of leptin than controls (Mantzoros *et al.*, 1999; Petridou *et al.*, 2000). This finding is consistent with the inverse association between BMI and premenopausal breast cancer. For prostate cancer, one case–control study (Lagiou *et al.*, 1998) showed no association with risk of prostate cancer or benign prostatic hyperplasia. However, the results from one prospective study suggested a possibly non-linear relationship of prostate cancer with plasma leptin concentration, with an increased risk only for moderately elevated leptin levels but not for the highest levels (Stattin *et al.*, 2001).

Platelet-derived growth factor (PDGF) is a potent mitogen for a variety of cells, and may be associated with cancer occurrence (Ross *et al.*, 1993). PDGF can also potentiate the action of growth factors such as IGF-I. Initiation of an exercise programme has been observed to cause eventual decrease in platelet responsiveness and aggregation (Rauramaa *et al.*, 1986; Sinzinger & Virgolini, 1988; Davis *et al.*, 1990). However, there have been no direct observations on a possible relationship between PDGF and cancer risk.

Prostaglandins have been associated with tumour growth in animal studies (Tutton & Barkla, 1980). Prostaglandin F_2 alpha inhibits tumour growth in the colon and increases gut motility; prostaglandin E_2 decreases colonic motility and increases the rate of colonic cell proliferation, especially in cancer cells (Bennett *et al.*, 1977; Tutton & Barkla, 1980). Strenuous physical activity appears to increase levels of prostaglandin F2 alpha and inhibit synthesis of prostaglandin E_2 (Demers *et al.*, 1981; Rauramaa *et al.*, 1984). In a cross-sectional analysis, Martinez *et al.* (1999b) observed that changes in both BMI and physical activity were associated with prostaglandin E_2 in rectal mucosa. An increase in BMI from 24.2 to 28.8 kg/m^2 was associated with a 27% increase in prostaglandin E_2 and an increase in activity level from 5.2 to 27.7 MET-hours per week was associated with a 28% decrease in prostaglandin E_2. The association of mucosal prostaglandin levels with cancer risk has not been studied directly, however.

Other mechanisms

There are several other hypothesized mechanisms of cancer occurrence that could explain associations of energy balance and physical activity with cancer occurrence. Except for a strong relationship between gastro-oesophageal reflux and oesophageal adenoma, however, the associations of these factors with cancer etiology are still largely unsubstantiated by direct observations in humans. Nevertheless, they are presented as potential explanations of etiological pathways and as areas for future research.

Gastro-oesophageal reflux

A number of epidemiological studies have shown a strong association between frequent gastro-oesophageal reflux and risk of Barrett's oesophagus and oesophageal adenoma. Relative risk estimates for usual BMI values ranged from 5.5 to 43.5 (Chow *et al.*, 1995; Lagergren *et al.*, 1999b; Farrow *et al.*, 2000). The use of medications that relax

the lower oesophageal sphincter has also been also found to increase the risk of oesophageal adenoma (Lagergren *et al.*, 2000). As described earlier in this chapter, gastro-oesophageal reflux disease is also strongly associated with BMI, and these observations provide evidence for gastro-oesophageal reflux as a mechanism relating obesity to oesophageal adenoma risk.

Intestinal transit time

A mechanism that might mediate the protective effects of physical activity against colorectal cancer is a reduction of gastrointestinal transit time (Holdstock *et al.*, 1970). Physical activity may shorten the faecal transit time through increased vagal tone and thus increased peristalsis. Reduced transit time would reduce the period of contact between carcinogens and colonic mucosal cells. Moderate-level activities such as walking or a training programme lead to a decreased transit time, resulting in increased propulsion of colonic contents through the colon (Cordain *et al.*, 1986; Koffler *et al.*, 1992). However, not all studies have found that physical activity reduces bowel transit time (Coenen *et al.*, 1992).

Immune function

Evidence for the potential of the immune system to destroy tumour cells and prevent tumour growth is compelling (Hoffman-Goetz, 1998; Nieman & Pedersen, 1999; Woods *et al.*, 1999). The immune surveillance theory hypothesizes that malignant cells survive in part because of impaired immune attack, due to either absence of immunogenicity (e.g., lack of tumour antigen expression) in the tumour cells or depressed immune response in the host system (Burnet, 1970). Immune-compromised individuals tend to show an excess of lymphomas, skin cancers and some other cancers (Penn, 1994; Schulz *et al.*, 1996; Schenkein & Schwartz, 1997), but the role of immune function in those cancers for which risk is associated with excess body weight and physical inactivity is not established.

There is little epidemiological data linking immune function and cancer in the general population. One recent cohort study of 3625 Japanese persons aged 40 years and older found that individuals with lower natural cytotoxic activity of blood lymphocytes had increased risk of cancer (all sites combined) compared with individuals having high activity (Imai *et al.*, 2000). The assays were performed at study entry and follow-up amounted to 11 years.

Bile acid metabolism

Physical activity and weight control may also induce favourable effects on bile acid levels in humans. A decrease in the ratio of secondary to primary bile acids has been observed in obese patients after treatment with subcaloric diet and graded physical activity (Kadyrova & Shakieva, 1986). Bile acids have been observed to influence the growth and proliferation of colonic cells (Bernstein *et al.*, 1999).

Summary

In conclusion, several effects of weight, weight control and physical activity have been linked with cancer risk in epidemiological studies. Findings on the association of metabolic and sex hormones and etiology of several cancers are intriguing. Data on links between immune function and the cancers most strongly related to weight and physical activity are not available and other potential mechanisms have not yet been supported by observational data.

Experimental studies

Experiments using animal models can provide information relevant to the mechanisms in human subjects in ways that are not otherwise possible. In identifying studies for review here, it was considered essential that mechanisms were evaluated within the context of experiments in which a cancer end-point was also studied. This approach has the advantage of increasing the likelihood of establishing causality, while being accompanied by the disadvantage of excluding some potentially relevant studies.

Weight control

Mechanistic considerations will be focused on following topics: carcinogen metabolism, DNA damage and repair, tissue size homeostasis which includes consideration of cell proliferation and apoptosis as well as the regulation of the relevant cellular machinery that carries out these processes, angiogenesis, modulation of immune function, and other mechanisms. Within these broad categories, the effects of energy restriction (or dietary restriction, as noted) on hormones and growth factors are reviewed. It should be emphasized that the operational division of carcinogenesis into stages is a useful tool for the investigation of this disease process, although the distinction between stages is in many respects arbitrary. Mechanisms generally considered to operate during initiation are likely to also affect post-initiation events and similarly, mechanisms that are described as post-initiation events clearly affect the process of initiation.

Effects on the initiation phase of carcinogenesis

Energy restriction has been reported to inhibit the initiation phase of the carcinogenic process, but a lack of effect on tumorigenesis has been noted in some model systems. Energy restriction (30–40%) before exposure of C3H/He male mice to 3 Gy of whole body X-radiation reduced the subsequent occurrence of myeloid leukaemia (Yoshida *et al.*, 1997). Energy restriction (50%) also reduced, to a limited extent, DMBA-induced mammary carcinogenesis when the restriction was imposed before and for a short time after carcinogen

administration (Sylvester *et al.*, 1982) and energy restriction (25%) has been reported to inhibit colon tumorigenesis induced by a carcinogen requiring metabolic activation, methylazoxymethanol acetate, but not by the direct-acting carcinogen MNU (Pollard & Luckert, 1985). However, energy restriction has been reported to have no effect on the initiation phase of skin tumorigenesis in Sencar mice following a single application of DMBA (Birt *et al.*, 1991) or in NMRI mice after chronic dermal application of DMBA (Fischer & Lutz, 1994). Effects of energy restriction on phase I and II metabolism and on DNA damage and repair mechanisms could account, at least in part, for the variable responses to carcinogenic insult when animals are energy-restricted during cacinogenic initiation.

Modulation of phase I drug-metabolism systems – cytochrome P450 enzymes

Energy and/or dietary restriction alters the activities of drug-metabolizing enzymes in a number of tissues, including liver, lung, kidney and testis, and it modulates the formation of carcinogen–DNA adducts in carcinogen-treated animals (see section on intermediate biomarkers in this chapter). Restriction has been observed to reduce the metabolic activation of aflatoxin B_1 in liver, but to increase the activation of benzo[*a*]-pyrene in both rats and mice (Chen *et al.*, 1996; Chou *et al.*, 1993a,b, 1997). In these studies, both increases and decreases in the activities of specific CYP enzymes have been noted (see Table 50), and in general changes in enzyme activity have correlated with changes in detected levels of adducts as predicted by the CYP activity profile. There are species, strain and gender differences that appear to modulate the effect of dietary restriction on CYP activities and adduct formation (Manjgaladze *et al.*, 1993). However, a moderate level of dietary restriction also has been reported not to affect the activity of either phase I or phase II drug-metabolizing enzymes (Keenan *et al.*, 1996). Collectively, these data indicate that dietary restriction has the potential to modulate DNA-adduct formation following carcinogenic insult, but it is not possible to make generalizable predictions about the potential for these effects to be beneficial against carcinogenic initiation due to the complexity of the systems involved.

Modulation of phase II drug-metabolism systems – conjugating enzymes

The effects of energy restriction on the activities of phase II conjugating enzymes have not been extensively studied, and contradictory results have been obtained (Chen *et al.*, 1995; Keenan *et al.*, 1996; Leakey *et al.*, 1989), as summarized in Table 50. Consequently, it is not possible to make generalizable statements about effects that these changes are likely to have on the initiation stage of the carcinogenic process.

Decreased oxidative DNA damage and increased DNA repair/antioxidant enzymes

Damage to DNA that leads to mutations and/or chromosomal alterations in specific genes, e.g., proto-oncogenes and tumour-suppressor genes, is causally involved in the genesis of cancer. Agents that can induce DNA damage come from both exogenous and endogenous sources. Effects of energy restriction on the metabolism of potential DNA-damaging agents of exogenous origin have been discussed in the preceding paragraphs. The present section focuses on agents that are endogenously produced and more specifically on reactive oxygen species. Oxidative damage to DNA can be decreased by reducing the formation of reactive species, increasing the scavenging of reactive species by low-molecular-weight compounds such as glutathione and/or by antioxidant enzymes, and by increasing the rate of DNA repair and the fidelity of repair. Numerous studies have reported that dietary restriction affects these processes at levels of restriction that have been demonstrated to prevent tumour development in an array of experimental model systems. However, such information must be recognized to be indirect. No studies in experimental models have demonstrated a direct relationship between energy restriction, reduction of oxidative DNA damage, decreased mutations, and the prevention of cancer. Moreover, there is limited evidence to indicate that reactive oxygen species are essential for the promotion and progression of carcinogenesis in the model systems in which energy restriction has been shown to prevent cancer. Hence, while a reduction in DNA damage as a mechanism for cancer prevention is clearly biologically plausible, evidence that energy restriction prevents cancer by decreasing DNA oxidation is inferential.

Energy restriction has been shown to decrease the accumulation of oxidized bases in DNA. It also reduces oxidative damage to proteins and lipids (Youngman *et al.*, 1992; Shigenaga *et al.*, 1994). With respect to DNA damage, energy restriction has been shown to reduce levels of 8-hydroxydeoxyguanosine by 20–25% in rat liver DNA isolated from nuclei or mitochondria (Chung *et al.*, 1992) and in five different tissues of mice, namely skeletal muscle, brain, heart, liver and kidney (Sohal *et al.*, 1994a). The effects of energy restriction on another oxidized base, 5-hydroxymethyluracil, in DNA isolated from liver or mammary gland was also investigated in rats; dietary restriction (40%) resulted in statistically significant reductions (approximately 40%) of this base in both tissues (Djuric *et al.*, 1992). Evidence exists that implicates a reduction in the formation of reactive oxygen species (Sohal *et al.* 1994b) via the inhibition, by energy restriction, of mitochondrial state

Table 50. Effect of energy restriction on the activities of phase I and phase II drug-metabolizing enzymes

Species/strain (sex)	Tissue	Enzymes	Effect of energy restriction on activity	Reference
		Phase I		
Rat				
Fischer 344 (M)	Testis	CYP2A1	Decrease	Seng *et al.* (1996)
Fischer 344 (M)	Liver	CYP2C11	Decrease	Manjgaladze *et al.* (1993)
Fischer 344 (M) (late in life)	Liver	CYP2E1-selective 4-nitrophenol hydroxylase	Increase	Manjgaladze *et al.* (1993)
Mouse				
$B6C3F_1$(M)	Lung	CYP1A1	Increase	Chen *et al.* (1996)
DBA/2J or C57BL/6N	Liver	AHH CYP1A1-dependent EROD, CYP2B-dependent PROD	Increase	Cou *et al.* (1993b)
		Phase II		
Rat				
Fischer 344 (M)	Liver	GST towards 1,2-dichloro-4-nitrobenzene	Decrease	Leakey *et al.* (1989)
Fischer 344 (M)	Liver	UDP-glucuronyltransferase and sulfotransferase towards hydroxysteroids	No effect	Leakey *et al.* (1989)
Fischer 344 (M)	Liver	UDP-glucuronyltransferase towards bilirubin Gamma-glutamyltranspeptidase	Increase	Leakey *et al.* (1989)
Fischer 344 (M)	Liver	GST towards aflatoxin B_1-8-9-epoxide	Increase	Chen *et al.* (1995)

AHH, aryl hydrocarbon hydroxylase; EROD, ethoxyresorufin-*O*-deethylase; GST, glutathione-*S*-transferase; PROD, pentoxyresorufin-*O*-dealkylase

4 respiration, the state primarily responsible for the generation of superoxide. Besides effects on the production of reactive species, lower levels of oxidized DNA could result from increased scavenging of reactive oxygen species, but contradictory findings have been reported, showing increases or no clear-cut patterns of the effect of energy restriction on activity of the antioxidant enzymes superoxide dismutase (SOD), catalase and glutathione peroxidase (Rao *et al.*, 1990; Sohal *et al.*, 1994b).

Enhancement of DNA repair mechanisms has been reported in response to 40% dietary restriction with or without supplementation. Ultraviolet-induced unscheduled DNA synthesis was found to be increased (Weraarchakul *et al.*, 1989) and O^6-methylguanine DNA-methyltransferase activity to be elevated (73%) by restriction (40%) (Lipman *et al.*, 1989). However, effects of restriction on the activities of enzymes that repair specific oxidized bases have not been reported. Finally, one study has shown that the fidelity of DNA repair by certain polymerases purified from liver is increased in dietary-restricted (40%) mice (Srivastava *et al.*, 1991).

Effects on the post-initiation (promotion/progression) stage of carcinogenesis

Most studies on effects of energy restriction in the prevention of cancer using experimental models have found inhibition of the post-initiation stage of the disease process; this stage is

also referred to as promotion or progression.

Tissue size homeostasis

The processes of clonal expansion and selection of transformed foci of cells in a tissue can occur only if a dysequilibrium exists between the rates of cell proliferation and cell death by apoptosis such that abnormal cells can accumulate in excess of their non-transformed neighbours (Thompson *et al.*, 1992). Several laboratories have reported that dietary restriction (20%) decreases the rate of cell proliferation and increases the rate of apoptosis (Grasl-Kraupp *et al.*, 1994; James & Muskhelishvili, 1994; Dunn *et al.*, 1997; Hikita *et al.*, 1997; Zhu *et al.*, 1999a). The directions of both effects are considered beneficial in terms of cancer prevention. By inducing levels of apoptosis, which can occur independently of wild-type *p*53 activity (Dunn *et al.*, 1997), the potential for deletion of damaged and pre-malignant cells from a tissue is enhanced. Data relating to the effects of energy restriction on each of these processes is presented in the following sections.

Inhibition of cell proliferation: Since most *in-vivo* assessments consider synthesis of DNA as synonymous with cell proliferation, they are here considered as one. Three general statements can be made about the effects of energy restriction on cell proliferation. First, in the many tissues and organs examined in energy-restricted animals, a reduction in the absolute number of cells present in a given tissue is uniformly observed. In some tissues, the reduction in cell number is directly proportional to body weight such that the cell number in an organ or tissue per 100 g body weight is essentially the same in dietary-restricted and *ad-libitum*-fed mice or rats (James & Muskhelishvili, 1994; Zhu *et al.*, 1999a). Second, the inhibitory effect of energy restriction on cell proliferation is constitutively expressed, i.e., it is non-specific and the magnitude of suppression is directly proportional to the degree of energy restriction (Lok *et al.*, 1990). Both normal and transformed or premalignant cell populations are affected (Grasl-Kraupp *et al.*, 1994; Dunn *et al.*, 1997; Zhu *et al.*, 1999a). Third, the inhibitory effect of energy restriction has been seen in most tissues that have been evaluated, although some investigators have not observed an effect (Merry & Holehan, 1985; Lok *et al.*, 1990). In the colon, energy restriction has been reported to reduce the activity of ornithine decarboxylase and mucosal protein tyrosine kinase activity, which would be consistent with decreasing the potential of cells to transit the cell cycle (Kumar *et al.*, 1990).

Cell cycle regulation: The evidence presented in the previous paragraph implies that energy restriction arrests the passage of cells through the cell cycle. The cells are likely to be arrested in the G1 phase of the cell cycle (Lu *et al.*, 1991). Female rats with 40% restricted energy intake had increased activity of the cyclin-dependent kinase inhibitor, P27, a member of the Cip/Kip family of kinase inhibitors (Zhu *et al.*, 1999b). High levels of P27 have been associated with arrest of cells in the G0/G1 phase of the cell cycle, at least in part via the inhibitory effect of P27 on the activity of the cdk2–cyclin E complex. Additionally, a lower percentage of mammary epithelial cells from energy-restricted animals stained positive for cyclin D1; this also is consistent with arrest of cells in the G0/G1 phase of the cycle as a result of a reduced capacity to initiate phosphorylation of the retinoblastoma protein (Rb), which is required for cells to traverse the G1/S transition in the cell cycle (Sherr, 2000). An associated issue is whether the effects on cell-cycle regulatory molecules are direct or are mediated by events upstream of cell cycle machinery. No data were available concerning direct effects of energy restriction on these cell-cycle molecules. However, three reports indicate inhibitory effects of energy restriction on protein kinase C isozymes α and ζ in epidermal and pancreatic cells (Birt *et al.*, 1994b, 1996; Nair *et al.*, 1995); these could be involved in signal transduction events that modulate cell proliferation. Moreover, energy restriction (40%) has also been reported to inhibit signalling down the mitogen-activated protein kinase (MAPK) pathway (Liu *et al.*, 2001). In particular, tumour promoter induction of the specific MAPK extracellular response kinase (ERK 1,2) was selectively inhibited in the epidermis of energy-restricted mice, while JNK and p38 kinase were not influenced. This inhibition may be particularly relevant to the prevention of skin tumours by energy restriction because ERK 1,2 induction directly activates the c-fos gene and indirectly activates the c-jun gene. These two genes are constituents of the transcription factor AP-1, induction of which by tumour promoters is fundamental to carcinogenesis.

Induction of apoptosis: Apoptosis is a means of deleting cells from a tissue in the absence of a significant inflammatory response. Apoptosis is induced in response to physiological, pharmacological and toxic stimuli. Either chronic energy restriction or acute fasting can induce apoptosis. Three laboratories have reported the induction of apoptosis in liver by either fasting or energy restriction (Grasl-Kraupp *et al.*, 1994; James & Muskhelishvili, 1994; Muskhelishvili *et al.*, 1995; Hikita *et al.*, 1997, 1999). It appears that constitutive rates of apoptosis are elevated but that preneoplastic hepatic cell populations are more sensitive to the apoptotic stimulus than are non-transformed hepatocytes. Whereas fasting was associated with a transient reduction in the number and volume of altered hepatic foci (Hikita *et al.*, 1999), chronic energy restriction was reported to cause a permanent reduction in the number of hepatic adenomas and carcinomas induced in comparison to controls

fed *ad libitum*, due to deletion of initiated hepatocytes (Grasl-Kraupp *et al.*, 1994). Energy restriction has also been reported to enhance rates of apoptosis in focal hyperplasia in the bladder (Dunn *et al.*, 1997) and in premalignant lesions in the mammary gland (Zhu *et al.*, 1999a). Induction of apoptosis has been noted to account for the decreased cellularity of the thymus and spleen in energy-restricted mice (Poetschke *et al.*, 2000), and under these circumstances the T-cell subsets had higher levels of plasma membrane Fas receptor and Fas ligand, and increased annexin-V positivity (Reddy Avula *et al.*, 1999). The authors suggested that these conditions reflect an increased potential for apoptosis.

Cell death machinery: While several studies have determined that energy restriction induces apoptosis, there have been no reports of which initiator caspases are activated by energy restriction, or of the signalling events that result in caspase activation. Nonetheless, the work cited above indicates that a death receptor pathway may be involved (Reddy Avula *et al.*, 1999).

Angiogenesis : The process of vascularization is intimately involved in regulating tissue size homeostasis. In order to support new growth, it is essential for neovascularization to occur, a process referred to as angiogenesis. Many findings indicate that energy restriction is likely to have an effect on this process. One report shows that energy restriction inhibits the progression of a transplantable prostate cell line. Inhibition of angiogenesis accompanied by reduced levels of vascular endothelial growth factor (VEGF) was one of the responses observed in energy-restricted animals that were inoculated with prostatic tumour cells (Mukherjee *et al.*, 1999). The authors suggested that the inhibition of angiogenesis by energy restriction protected animals against tumour development in this model system.

Hormones and growth factors

Modulation of insulin and insulin-like growth factors (IGFs): As described earlier in this chapter, energy-restriction in rodents prevents DMBA-induced mammary tumorigenesis in proportion to the degree of restriction imposed. In the same studies, energy restriction also resulted in a reduction in plasma insulin levels that was proportional to the degree of restriction imposed (Klurfeld *et al.*, 1989a, b). The development of DMBA-induced mammary tumours is also inhibited by alloxan-induced diabetes and alloxan- or streptozotocin-induced diabetes in rats causes a regression of 60–90% of DMBA-induced mammary tumours (Heuson & Legros, 1972; Cohen & Hilf, 1974; Hilf *et al.*, 1978; Gibson & Hilf, 1980). Tumour growth was restored and tumour latency reduced upon insulin administration to diabetic rats.

Energy restriction has also been reported to prevent the development of DMBA-induced mammary tumours in genetically obese LA/N-cp female rats. In both the obese animals and their genetically normal lean controls, energy restriction led to low plasma insulin levels. The authors speculated that insulin might be mediating the effect of energy restriction on tumour occurrence in this model system (Klurfeld *et al.*, 1991).

The effects on IGF metabolism of levels of energy restriction that inhibited tumour development have been investigated in four studies. Ruggeri *et al.* (1989) reported that a level of energy restriction that inhibited DMBA-induced mammary tumorigenesis reduced circulating levels of insulin and IGF-I, but not those of IGF-II. Initially, levels of both insulin and IGF-I were reduced, but only the effect of energy restriction on insulin persisted. Two studies found that energy restriction inhibited the development of either leukaemias or bladder cancer (Hursting *et al.*, 1993; Dunn *et al.*, 1997). The inhibitory effects on tumour development were accompanied by reductions in circulating levels of IGF-I. Both studies found rates of cell proliferation to be reduced in restricted animals, and in the bladder cancer model, the rate of apoptosis was markedly elevated in focal hyperplasias in energy-restricted animals. Administration of IGF-I to restricted animals restored the rates of proliferation and apoptosis to those observed in animals fed *ad libitum* (Hursting *et al.*, 1993; Dunn *et al.*, 1997). It was proposed that the effects of dietary restriction are mediated via changes in the availability of IGF-I, which modulates tissue size homeostasis by increasing cell proliferation and decreasing the rate of apoptosis. This hypothesis has significant biological plausibility given the role of IGF-I as a potent mitogen and as a survival factor (Kari *et al.*, 1999).

Modulation of adrenal cortical steroids: As early as 1948, a role was hypothesized for the adrenal gland in mediating the tumour-preventive effects of energy restriction (Boutwell *et al.*, 1948). In mice, adrenalectomy has been shown to abolish the protective activity of dietary restriction against chemically induced tumorigenesis in the skin and lung (Pashko & Schwartz, 1992, 1996). Elevated levels of corticosterone also accompanied dietary restriction in animals with an intact adrenal gland. The hyperplastic response normally observed during the carcinogenic initiation–promotion protocol was inhibited by energy restriction, but this inhibitory effect was abolished by adrenalectomy (Pashko & Schwartz, 1992). In rats, energy restriction leads to increased urinary excretion of corticosterone, and urinary corticosterone concentration was inversely associated with tumour multiplicity (Zhu *et al.*, 1997). In these studies, the authors hypothesized a causal role for adrenal cortical steroids in accounting for the cancer-preventive activity of energy restriction. Consistent with this observation, the inhibition of mouse skin carcinogenesis in the DMBA-initiation/-TPA-

promoted Sencar mouse model by energy restriction was paralleled by reductions in protein kinase C α and ζ (Birt *et al.*, 1994b, 1996). Subsequently, mice were administered corticosterone in the drinking-water in a manner that elevated circulating corticosterone levels to an extent similar to that observed with energy restriction (Birt *et al.*, 2001). The pattern of reduced epidermal expression of protein kinase C isozymes α and ζ and elevation of isozyme η was strikingly similar to the alterations observed in the epidermis of dietary energy-restricted mice.

The role of glucocorticoid hormone in the prevention of rodent carcinogenesis has been studied (Yaktine *et al.*, 1998; Birt *et al.*, 1999); elevated glucocorticoid hormone levels have been reported to be associated with prevention of carcinogenesis and an intact adrenal gland is claimed to be essential for prevention of cancer by dietary restriction (Pashko & Schwartz, 1992, 1996). In contrast to findings in rats (Morimoto *et al.*, 1977; Armario *et al.*, 1987) and humans (Chiappelli *et al.*, 1991; Kennedy *et al.*, 1991), underfeeding hamsters did not result in elevated levels of glucocorticoid hormones. This hormonal response of hamsters may have been a factor in the inability of energy restriction to prevent ductular pancreatic carcinogenesis in the hamster model (Birt *et al.*, 1997).

Modulation of sex steroids: The hypothesis that energy restriction might act as a pseudohypophysectomy has its origins in early work in the field (Boutwell *et al.*, 1948). The relevance of the sex steroids estrogen and progesterone to the development of cancer has been covered in Chapter 4 and earlier sections of this chapter. The number of studies that have examined the effects of energy restriction on sex hormone function in parallel with its effects on the development of experimentally induced breast cancer is fairly limited. Sylvester *et al.* (1981) and Sarkar *et al.*, 1982) both observed suppression of estrogen and prolactin secretion under conditions of energy restriction that inhibited mammary tumour development, but Sinha *et al.* (1988) failed to find differences in plasma estradiol levels at different stages of the estrous cycle or disruption of estrous cycling in rats subject to energy restriction. While such effects are not anticipated from the human findings reviewed in this volume, they imply that other mechanisms are likely to be involved. Conditions of energy restriction can be defined that inhibit mammary carcinogenesis with or without an effect on the hypophyseal–pituitary–ovarian axis. This finding is supported by the work of Harvell *et al.* (2001a), who found no effect of energy restriction on circulating 17β-estradiol in a rat model of estradiol-induced mammary carcinogenesis.

In reviewing the literature on this topic, the Working Group noted a lack of discussion on which experimental tumour systems model postmenopausal breast cancer. Therefore, although the mammary carcinogenesis model systems that have been studied show sensitivity to ovarian steroids, ovariectomy and anti-estrogen therapy, it is not clear how these observations relate to the epidemiological findings on the role of weight control and physical activity in postmenopausal breast cancer reviewed in the first part of this chapter. It appears possible to amplify the cancer-preventive effects of energy restriction on hormone-sensitive target organs by modulating the activity of the hypophyseal–pituitary–ovarian axis, but effects on these hormones do not appear to be obligatory in accounting for the cancer-preventive activity of energy restriction in such model systems.

Other mechanisms

Alterations of energy metabolism: Energy restriction produces an effect on intermediary metabolism in the liver that favours the role of glucagon in regulation of glycolysis and glucose synthesis, while limiting the role of insulin. This results in higher glucose synthesis and lower glucose catabolism (Feuers *et al.*, 1989). The former effect was interpreted as providing for the efficient support of peripheral tissues and the latter a level of energy production necessary for self-maintenance. Using c-DNA array technology to characterize patterns of change in gene expression with ageing and the effects of energy restriction in a post-mitotic tissue (mouse muscle), Lee *et al.* (1999c) showed that energy restriction alters the expression of a number of genes involved in energy metabolism.

The potential interaction between effects of energy restriction on energy metabolism, changes in energy metabolism that occur in target cells following carcinogenic insult, and the inhibition of cancer by energy restriction has received limited attention. However, there is evidence that biologically plausible relationships exist that may underline, at least in part, the protective activity of energy restriction against cancer. Zhang *et al.* (1998) studied energy metabolism during AOM-induced colon carcinogenesis in male Sprague Dawley rats. They concluded that colonocyte energy metabolism differs between AOM-treated rats and saline controls and that it changes during tumorigenesis. A positive relationship between intracellular energy status and patterns of cell proliferation was observed. Using a yeast model for energy restriction, Lin *et al.* (2000) found that limiting the availability of glucose led to activation of a gene-silencing pathway by NAD+. The existence of homologues of these genes in mammalian cells remains to be established. It is still unclear whether effects of energy restriction on the availability of high-energy molecules (ATP, NADH and NADPH) play either a direct role in inhibiting the development of cancer by silencing genes involved in tumour initiation, promotion or progression, or an indirect role by regulating cell

proliferation, apoptosis and/or angiogenesis.

Prevention of obesity: Data from experimental studies indicate that prevention of obesity is likely to affect endocrine function, i.e., insulin sensitivity and circulating levels of hormones such as estrogen. It could also affect levels of DNA damage by exogenous as well as endogenous agents. These topics have been reviewed above and will not be further discussed.

Modulation of immune function: The effects of energy restriction on immune function have been investigated most extensively in studies of the ageing process. In general, energy restriction has been reported to improve cell-mediated immune function by preventing age-related declines in activity (Cheney *et al.*, 1983; Weindruch *et al.*, 1986; Fernandes *et al.*, 1997; Frame *et al.*, 1998). Specific effects on CD4+ and CD8+ T cells and on natural killer cell activity have been reported as well as on T-lymphocyte proliferation. While experiments investigating the effects of dietary restriction on ageing-related changes in immune function have also noted the effects on spontaneous tumour occurrence, little effort has been made to determine if modulation of immune function is involved in the cancer-preventive activity of energy restriction. Most studies have used models in which tumour cells were inoculated and effects of energy restriction on tumour metastasis and immune function were measured. In three reports, effects of energy restriction on cell-mediated immunity were noted (Ershler *et al.*, 1986; Hodgson *et al.*, 1996, 1997), but in one of these (Hodgson *et al.*, 1996), energy restriction was associated with an increase in metastasis. Thus, while it is biologically plausible that effects of energy restriction on immune function could, at least in part, account for its cancer-preventive activity, experimental data remain limited and inconclusive.

Physical activity

There are a number of plausible mechanisms by which physical activity may prevent the development of cancer, but data in support of these mechanisms remain limited. In experimental tumour models, most work has focused on inhibition of the post-initiation (promotion and progression) stages of carcinogenesis by physical activity. However, it appears that physical activity can also affect the process of initiation (see the section on experimental studies of physical activity earlier in this chapter).

Immune status and function

Considerable attention has been directed to the hypothesis that physical activity prevents cancer in humans by enhancing immune function. Studies of this hypothesis in experimental tumour models have been limited to investigating the effects of physical activity in transplantable tumour systems. Thus, exercise-mediated effects on the immune system during either the initiation or the promotion phase of experimentally induced carcinogenesis have not been investigated.

The immune mechanisms most likely to be involved in protection against cancer include exercise- or training-induced increases in the number and/or activity of lymphokine-activated killer cells, tumour-infiltrating macrophages and/or activated natural killer cells. Since most of the immediate immune responses to exercise are relatively short-lived, susceptibility to cancer is more likely to be affected by training-induced changes in resting function of the immune system than by the immediate responses to a bout of exercise (Shephard & Shek, 1995). Many investigators have reported effects of various exercise regimes and/or training programmes on components of the immune system, but only a few studies have combined these measurements with data on the effects of the physical activity regime on a tumour outcome. Hoffman-Goetz *et al.* (1992) exercised C3H mice on a treadmill and inoculated them with CIRAS 3 tumour cells at four weeks into the training protocol. At eight weeks of training, exercise was significantly associated with increased natural killer (NK) cytotoxicity against tumour targets *in vitro*, but this effect was observed only in animals without visible lung tumours. Consequently, the authors were doubtful about the physiological significance of exercise-induced changes in immune function on tumour progression. Hoffman-Goetz *et al.* (1994) also compared the effects of exercise on an activity wheel with those due to treadmill exercise on the occurrence of pulmonary metastases in female BALB/c mice inoculated intravenously with the MMT 66 tumour cell line. In general, exercise tended to increase NK activity and lymphokine-activated killer (LAK)-mediated cytotoxicity; however, no effect of exercise on lung metastasis was observed. Thus, although exercise training influences natural immune cytotoxic mechanisms *in vitro*, this may not translate into clinically significant changes in tumour burden (Hoffman-Goetz *et al.*, 1994). Woods *et al.* (1994) studied the effects of treadmill exercise on phagocytic capacity of intratumoural phagocytes in C3H/He male mice inoculated subcutaneously with SCA-1 mammary adenocarcinoma cells. While moderate exercise increased phagocytic capacity, no effect of exercise on tumour incidence or tumour size was observed. Jäpel *et al.* (1992) also reported enhanced phagocytosis of macrophages in tumour-bearing animals trained on a treadmill; this effect strongly depended on the duration and onset of the training programme.

Sex hormones

Data from human studies suggest that physical activity could prevent cancer by an endocrine route through an effect on sex steroids. Cohen *et al.* (1993) examined this possibility in carcinogenesis studies in female

Sprague-Dawley rats given access to activity wheels. Using DMBA to induce mammary tumours, access to exercise was associated with lower tumour occurrence; the nature of the protective activity depended on the dose of carcinogen. No difference in cytosolic estrogen receptor levels in the induced tumours was noted between animals that were sedentary and those that were exercised. The authors considered these data to cast doubt on the idea that physical activity selects, via an endocrine effect, for estrogen-non-responsive tumours. Cohen *et al.* (1991) observed that voluntary exercise on activity wheels reduced yields of MNU-induced mammary tumours and delayed time of tumour appearance (see page 185). They found no effect of wheel-running on circulating bioactive or immunoreactive prolactin and deduced that this cast doubt on mediation of the cancer-preventive effect of exercise by prolactin.

Insulin/glucose

Effects of exercise on insulin and/or IGF-I have been reported in two experimental tumour systems. Kazakoff *et al.* (1996) studied the effect of access to an activity wheel on induction of pancreatic cancer in female Syrian hamsters given an injection of BOP. They found exercise to have no effect on tumorigenesis, despite the fact that animals with access to exercise had significantly lower levels of circulating insulin, though unchanged plasma IGF-1 levels. The authors concluded that since exercise did not modulate tumour incidence, the effects of exercise on insulin probably do not mediate its effect on tumour development. While using a model not directly applicable to cancer prevention, Daneryd *et al.* (1990) studied the effects of access to an activity wheel in female Wistar Furth rats implanted with a transplantable tumour. Tumour-bearing exercised animals had higher insulin sensitivity and the exercised animals had a smaller tumour mass, the magnitude of reduction depending on the type of tumour implanted.

Other mechanisms

Various other plausible mechanisms could account for the cancer-preventive effects of physical activity (Cohen *et al.*, 1992). However, no experimental data were available to the Working Group for any exercise protocol known to prevent cancer in relation to the following mechanisms: stimulation of colonic peristalsis, altered prostaglandin production, increased endorphin production, altered adiposity/fat distribution (obesity), enhanced free-radical/antioxidant functions.

What counts as moderate physical activity ?

- **Raking leaves**
- **Digging in the garden**
- **Walking the dog**
- **Mowing the lawn**
- **Climbing stairs**
- **Dancing**
- **Cleaning windows**
- **Household chores**
- **Swimming**
- **Hiking**
- **Shovelling snow**
- **Riding a bike**