One explanation for the increasing incidence of cancers in developing countries has been the hypothesis that a chronic state of positive energy balance promotes tumor growth. Tannenbaum (1940a,b) first explored this hypothesis in animal models and demonstrated that both increased calories and fat increased the occurrence and number of breast cancer tumors in mice. Similarly, epidemiologic studies in humans in the 1970s demonstrated that heavier women were at increased risk of breast and endometrial cancer (De Waard et al., 1974; Blitzer et al., 1976). Other population-based studies in the early 1980s suggested that risk increased with increasing weight for several other cancer sites, specifically colon, prostate, gallbladder (among women), and kidney (Lew and Garfinkel, 1979; Hartz et al., 1984; Garfinkel, 1986). Since then, numerous epidemiologic studies have examined the association of weight and other anthropometric measures with cancer incidence and have explored potential biological mechanisms to explain observed associations. The majority of these studies have focused on breast, colon, endometrial, renal cell, esophageal/gastric, and prostate cancer; limited data are available on body size associations with other cancer sites.

The aim of this review is to provide a comprehensive overview of the state of scientific evidence for the association between obesity-related risk factors and cancer, with a focus on those cancers with sufficient evidence for review: those of the colon, rectum, esophagus/gastric cardia, renal cell, endometrium, ovary, breast, prostate, thyroid, lung, and head and neck. The specific objectives of this review are:

- Summarize the epidemiologic literature for the association between cancer risk and obesity-related measures of weight or body mass index (BMI; defined most commonly as weight in kilograms [kg] divided by height in meters squared), fat deposition patterns (commonly approximated by waist circumference or by the ratio of waist-to-hip circumferences [WHR] or by ratios of truncal to extremity skinfolds), and weight change;
- Highlight gaps in scientific knowledge for the association of obesity-related factors and cancer risk;
- Identify the possible underlying biological mechanisms for these associations;
- Comment on areas for future research; and
- Estimate the public health impact of obesity on cancer risk at the international level.

Because of space limitations, the epidemiologic evidence on height and cancer risk is not included in this review but has been well summarized in several previous reviews (Ballard-Barbash, 1999; Gunnell et al., 2001).

METHODS

A search was conducted on MEDLINE and PUBMED for all publications on weight, body mass index, anthropometric factors, and specific cancers in human populations and was supplemented by a manual search of all major relevant journals. The literature search included all publications up to February 2003. Studies included in this review focused on some aspect of anthropometric risk factors in relation to cancer risk for the cancers noted above. Major review papers or books were also identified and reviewed. Summary figures of risk estimates for the highest compared to lowest quintile of BMI and the major cancer sites were generated. Because of the very large number of studies in breast cancer, studies with at least 100 cases each of pre- and postmenopausal breast cancer cases are included in the breast cancer figures. Because of differences in risk for colon and rectal cancer and the limited number of studies on rectal cancer alone, only data on colon cancer were summarized in the colon cancer figure. Biological mechanisms potentially involved in the association between obesity and specific cancers were summarized in a table. In addition, population attributable risks estimated for the European Union by Bergström et al. (2001) were compared to current estimates for the United States and summarized in a table. A summary statement for each cancer site was developed following the criteria for convincing, probable, possible, and no association as summarized in the 1997 World Cancer Research Fund and American Institute for Cancer Research (World Cancer Research Fund, 1997) report on Food, Nutrition and the Prevention of Cancer: A Global Perspective.

METHODOLOGIC AND MEASUREMENT ISSUES

Existing methods for assessing the etiologic and prognostic influences of energy balance and body size on cancer have limitations that should be considered when evaluating the epidemiologic evidence and planning future research. Briefly summarized, these limitations fall into three areas: validity of exposure assessment, difficulty of comparisons across studies, and insufficient sample sizes to explore fully the many factors that relate to body size and fat mass and that could potentially modify observed associations.

The measurement of anthropometric indices is generally well standardized and documented (Lohman et al., 1988; WHO, 1995). In fact, the standardization, accuracy, and reliability of these measures are better than for many other cancer-related exposures. Weight and height are the most standardized measurements and least subject to variability. More recent investigations have used interviewers to measure various anthropometric indices from study participants, hence reducing the possibility of random and systematic error. However, many studies of cancer etiology have relied on self-reported weight and height. Studies on self-reported height suggest a reasonable degree of accuracy with a bias in overreporting height that is somewhat greater in men compared to women and that increases with age (Rowland, 1990) or is limited to people over age 60 (Kuczmarski et al., 2001), presumably due to age-related loss in height. Studies on self-reported weight indicate the presence of significant misreporting at the extremes of weight, with heavier people underreporting and lighter people overreporting their weight (Rowland, 1990; Stevens et al., 1990; Must et al., 1993). Therefore, studies of chronic disease that rely on self-reported height and weight will underestimate the risk associated with these measures (Gunnell et al., 2000). Nonetheless, compared to estimates of correlation between reported versus measured assessment of other exposures, such as dietary intake, correlation coefficients between recalled and measured weight suggest that weight is recalled with a reasonable degree of accuracy. For example, in one U.S. study, correlations between reported and measured weights for
elderly subjects asked to recall weight currently and from 4 and 28 years previously were reported to be 0.98 for current, 0.94 for 4-year, and 0.82 for 28-year recall (Stevens et al., 1990). Measurement of skinfolds and circumferences is less reliable than the measurement of weight and height (Lohman et al., 1988; WHO, 1995). However, reliability is improved with standardization in measurement technique. It is not feasible to obtain these anthropometric measures from self-report. Waist circumference is currently considered to be the most convenient and simple measure of abdominal or central adiposity for epidemiologic research (WHO, 1995, 2000). Percent body fat can be estimated from bioelectric impedance but only has been reported in one study of cancer etiology (Lahmann, 2003). Bioelectric impedance is currently the most promising field method for estimating body composition in large epidemiologic studies because it is portable, inexpensive, easy to use, and highly precise. Issues related to use of different methods for estimating body composition for chronic disease epidemiology are well summarized by Baumgartner and colleagues (1995).

Comparison across studies is difficult because most studies have examined risk by quantile distributions (most commonly tertile or quartile) for the BMI or other anthropometric measures used. As the distribution of BMI varies across populations, these quantile groups are not comparable across studies, making comparison difficult. With increasing interest in understanding the risk for many chronic diseases by standard WHO BMI categories, investigators have begun to examine risk by these categories: underweight as BMI of less than 18.50, normal weight as BMI of 18.50–24.99, overweight as BMI of 25.00 or higher. This latter overweight category is further subdivided into four categories: preobese, 25.00–29.99; obese class I, 30.00–34.99; obese class II, 35.00–39.99; and obese class III, 40.00 (WHO, 2000). More recent meta-analyses have the ability to examine risk by these broad weight categories; however, analyses should not be limited to these categories as risk may vary within them, depending on the chronic diseases and the populations examined.

Research to date suggests often complex and varying associations of body size with different cancer sites. Although cancer as a whole now exceeds coronary artery disease as a cause of death in the United States population under age 85, the incidence of site-specific cancer is much lower than diseases such as diabetes mellitus and coronary artery disease, limiting the sample sizes of studies for less common cancers. Therefore, delineation of the association of body size and cancer requires site-specific studies, which can often be done only through multicollaborative efforts for less common cancers. Furthermore, as more factors are identified as potentially influencing body size and cancer associations, delineation of the underlying mechanisms requires further subgroup analysis, thereby increasing sample size requirements.

The “gold standard” technologies required, such as doubly-labeled water for measuring energy expenditure or computerized tomography for measuring body composition, are expensive, not easily portable, and, thus, not feasible for large samples. Therefore, it is not possible to directly measure positive energy balance in large epidemiologic studies of cancer risk or prognosis. In addition, although it is possible to estimate energy balance from its components—energy intake and expenditure—current methods to assess diet and physical activity rely on self-report of food intake and physical activity, a methodology with substantial reporting error. Consequently, because large epidemiologic studies cannot measure energy balance through either doubly-labeled water techniques or through accurate estimation of energy intake and expenditure from self-reports, the most valid measure of either persistent or recurrent states of positive energy balance is weight gain during adult life. Given findings from clinical metabolic research of complex interactions among different steroid hormones, such as sex steroids and insulin, ranging from receptor cross-reactivity to postreceptor potentiation, statistical modeling methods that allow for this complex interaction are needed and have not been used. In the future, statistical approaches for complex systems, including factor analysis and assessment of effect modification and interaction, may advance understanding of the metabolic factors underlying body size and cancer associations.}

**COLORECTAL CANCER**

**Summary of Findings**

Data from case-control and cohort studies provide convincing evidence of an approximately twofold increase in risk of colon cancer among men with a BMI of 30 or more. Risk estimates for men are most commonly reported to be about 2. Among women, less extensive data provide evidence of a probably increased risk of colon cancer from a high BMI with risk estimates usually between 1.0 and 1.5. Among obese women who are estrogen positive (defined as premenopausal or postmenopausal and taking hormone replacement therapy [HRT]), a twofold increase in risk has been reported. Most of the literature has found no association between BMI and rectal cancer. Meta-analyses that provide a more quantitative statement of the association across several studies have not been published.

**Overview**

Many aspects of the associations between body weight, obesity, and colorectal cancer have been examined. Colorectal cancer has been studied by examining risk associated with colon and rectal cancers combined, as well as for each site separately. Although many studies have examined associations with colon cancer, few have considered rectal cancer specifically. Additionally, unlike many cancers, associations between body size and the precursor lesion, adenomatous polyps, have been reported. Several consistent differences in associations by gender, site, and location within the colon have been observed. Strong associations have been observed for men than for women; for colon than for rectal cancer; and, within the colon, for distal than for proximal tumors.

Studies examining the associations between body size, obesity, and colorectal cancer have used many different indicators of body size. Most studies have relied on BMI, usually from several years before diagnosis. Few studies have used the current WHO criteria for overweight (BMI ≥ 25) and obesity (BMI ≥ 30), making comparisons and interpretations across studies difficult. Most studies have categorized BMI based on distribution in the population, and although the lower limit for the upper category of BMI is often near 30, at other times it is around 26. Limited data exist on waist and hip circumferences as indicators of fat pattern and its impact on colorectal cancer risk. Most studies focus on adult BMI, with little information available on weight change or early-life body size as possible predictors of risk. Because of differences in reported associations for colon and rectal cancer, evidence for these sites is summarized separately.

**Colon Cancer**

**Epidemiology**

Many studies have evaluated associations between body size and colon cancer, and reported associations have been fairly consistent across case-control and cohort studies. Studies that have examined associations with obesity report slightly stronger associations than those for overweight. For men, most studies report significant increased risk, with risk estimates of 2.0 or greater, although risk estimates range from 1.2 to 3.0 (Graham et al., 1978; West et al., 1989; Gerhardsson de Verdier et al., 1990; Le Marchand et al., 1992; Lee and Paffenberger, 1992a; Giovannucci et al., 1995; Caan et al., 1998; Singh et al., 1998; Schoen et al., 1999) (Figures 22–1a and 22–1b). Most studies have adjusted for important confounding factors, including physical activity, dietary intake, and smoking, although some report age-adjusted estimates of association only (Lund Nilsen and Vatten, 2001). Associations observed for women are generally weaker than those observed for men and are often not statistically significant. For women, risk estimates have generally ranged from 0.7 to 2.7 (Potter and McMichael, 1983; Graham et al., 1988; Kune et al., 1990; Bostick et al., 1994; Dietz et al., 1995; Le Marchand et al., 1997; Martinez et al., 1997; Caan et al., 1998; Singh et al., 1998; Ford, 1999; Terry et al., 2001, 2002). Some studies report a similar twofold increase in risk of colon cancer for both men and women for the highest BMI quantile examined (approximately 30) (West et al., 1989;
PART III: THE CAUSES OF CANCER

Cohort Studies: Population-Based
Lee and Paffenberger (1992a), USA, n=290
Le Marchand et al. (1997), USA, n=421
Chyo et al. (1996), USA, n=289
Giovannucci et al. (1996), USA, n=203
Singh & Fraser (1998), USA, n=59
Ford (1999), USA, n=104
Lund Nilsen and Vatten (2001), Norway, n=234

Case-Control Studies: Hospital-Based
Russo et al. (1998), Italy, n=687

Case-Control Studies: Population-Based
Graham et al. (1988), USA, n=205
Gerhardsson de Verdier et al. (1990), Sweden, n=233
West et al. (1989), USA, n=112
Kune et al. (1990), Australia, n=388
Caan et al. (1998), USA, n=1,095

A
Cohort Studies: Population-Based
Bostick et al. (1994), USA, n=212
Martineau et al. (1993), USA, n=293
Singh & Fraser (1998), USA, n=83
Ford (1999), USA, n=118
Terry et al. (2001), Sweden, n=291
Lund Nilsen and Vatten (2001), Norway, n=277
Terry et al. (2002), Canada, n=383
Terry et al. (2002), Canada, premenopausal, n=118
Terry et al. (2002), Canada, postmenopausal, n=104

Case-Control Studies: Population-Based
West et al. (1989), USA, n=119
Graham et al. (1988), USA, n=223
Gerhardsson de Verdier et al. (1990), Sweden, n=189
Kune et al. (1990), Australia, n=327
Caan et al. (1998), USA, n=688
Slatery et al. (2003), USA, estrogen+, n=301
Slatery et al. (2003), USA, estrogen-, n=576

B

Ford, 1999). Few studies have included African Americans. The one study reporting associations for African Americans was limited to 99 cases and reported no significant association between BMI and colorectal cancer (Dales et al., 1979).

Some studies have had sufficiently large sample sizes such that associations for proximal and distal colon tumors could be considered separately. Stronger associations for distal tumors than proximal tumors are often seen (Dietz et al., 1995; Martinez et al., 1997; Caan et al., 1998), although the study by Le Marchand et al. (1997) showed stronger associations with proximal rather than distal tumors, and the study of women by Terry et al. (2001) did not observe a significant association for either proximal or distal tumors. In a study by Le Marchand et al. (1992), the greatest risk associated with a high BMI was observed for sigmoid tumors, which most studies include as part of the distal colon.

Some studies have examined waist-to-hip ratio and colon cancer risk (Martinez et al., 1997; Caan et al., 1998; Russo et al., 1998; Schoen et al., 1999). Similar results have been observed from both case-control and cohort studies, and suggest that a higher WHR increases risk of colon cancer.

Biological Mechanisms and Tumor Mutations
Associations between body size and colon cancer risk may be modified by several factors. Interactions between BMI, physical activity, and hormones appear to provide the most insight into possible biological mechanisms. High levels of vigorous physical activity have been shown to modify the risk associated with obesity; for example, risk is not as markedly increased among obese men and women who are physically active (Lee and Paffenberger, 1992a; Le Marchand et al., 1997; Slattery et al., 1997). Interactions between obesity and estrogen or HRT may explain gender differences in risk associated with BMI (Terry et al., 2002). Studies have shown that being overweight or obese increases risk of colon cancer only among women who are premenopausal (Terry et al., 2002). In another study that examined
estrogen-positive women (defined as premenopausal or post-menopausal and taking HRT), risks associated with a high BMI were similar to associations observed in men, with risk estimates for a BMI of 30 or more being twofold greater than that of women who are lean (Slattery et al., 2003). However, women who were estrogen negative (defined as postmenopausal and not taking HRT) did not experience increased risk from being overweight or obese. In men it has been observed that, with advancing age, the risk associated with being overweight or obese declines (Slattery et al., 2003). This change in risk over time could be the result of declining androgen levels that operate in a similar fashion as estrogen in regulating risk associated with obesity. These interactions between physical activity and BMI, and estrogen and BMI, suggest that at least one way BMI may influence colorectal risk is through its influence on estrogen and insulin.

Evaluations of the association between BMI and colon cancer that have examined specific tumor mutations have provided insight into possible mechanisms of action and the role of body size in possible specific disease pathways. The few published studies suggest that BMI may be involved in several pathways. One study reported that an elevated BMI was associated with Ki-ras mutations in codons 12 and 13 (Slattery et al., 2001a). The BMI associations appeared to be more specific for Ki-ras mutations in women than in men. BMI appeared to be equally associated with tumors with and without p53 mutations (Slattery et al., 2002). Obesity was reported as being associated only with tumors that were stable (i.e., negative for microsatellite instability) in women, although in men, obesity was associated with both stable and unstable tumors (Slattery et al., 2001b).

Rectal Cancer

The small number of studies that have examined associations between body size and rectal cancer generally report results for few cases. From existing data it appears that body size is not associated with rectal cancer among men or women (Graham et al., 1988; Gerhardsson de Verdier et al., 1990; Dietz et al., 1995; Le Marchand et al., 1997; Russo et al., 1998; Terry et al., 2001). In contrast, one study of women reported reduced risk of rectal cancer among those with a BMI of more than 25 relative to those with a BMI of less than 22 (Potter and McMichael, 1986). Unlike colon cancer, studies of rectal cancer have not evaluated interactions between BMI and other indicators of body size with diet and lifestyle factors. This lack of examination of interaction is most probably because of the relatively limited number of rectal cancer cases available for analysis, making studies of interaction impracticable and problematic. Evaluation of BMI and other indicators of body size with specific mutations in tumors have not been reported.

Colorectal Adenomas

Studies evaluating the association between body size and the occurrence of adenomas have examined associations by polyp size and type. Most studies of colorectal adenomas have examined BMI alone and have observed similar associations as for colon cancer (Neugut et al., 1991; Shinichi et al., 1994; Davidow et al., 1996; Giovannucci et al., 1996). Some studies do not detect associations with adenomas and body size (Terry et al., 2001, 2002). In a study that included both cancer and adenomas, an increased risk with a high BMI was observed for large adenomas only, but not for colorectal tumors (Boutron-Ruault et al., 2001). Most studies have observed a 1.5- to 2.5-fold increase in risk of adenomas among the group with the highest BMI. A large WHR also has been associated with adenomas, with stronger associations being observed for larger adenomas (Kono et al., 1991; Shinichi et al., 1994; Kono et al., 1999). Similar to studies of rectal cancer, studies of adenomas have been limited in terms of examining interactions with other diet and lifestyle factors, primarily because of small sample sizes available to examine interactions. One study by Martinez et al. (1999) observed no differences in risk for adenomas among those with and without Ki-ras mutations.

ADENOCARCINOMAS OF THE ESOPHAGUS (AE) AND GASTRIC CARDIA (AC)

Summary of Findings

Data from case-control and cohort studies provide evidence of a probable and fairly consistent association of a twofold or greater increased risk of adenocarcinoma of the esophagus and gastric cardia from overweight and obesity. Most studies have evaluated risk using a BMI of around 30 or more as the upper level of BMI, although some studies use a much lower BMI as the upper level. The increased risk associated with obesity has been observed in both men and women. Meta-analyses that provide a more quantitative statement of the association across several studies have not been published.

Epidemiology

The incidence of adenocarcinoma of the esophagus and gastric cardia has risen dramatically in the past two decades in developed nations (Li and Morbahan, 2000; Walther et al., 2001). For reasons not entirely clear, body size and obesity are associated with AE and AC, with the increases in the incidence of these diseases paralleling the increases in obesity observed in Western cultures.

An important feature of the observed associations between AE and AC and body size is that they are limited to adenocarcinomas and generally are not observed for squamous cell cancer or other histological types (Vaughan et al., 1995; Chow et al., 1998; Lagergren et al., 1999). However, one study reported a sixfold increased risk of squamous cell esophageal tumors and no increased risk of AE or AC adenocarcinomas among individuals with a high BMI (Kabat et al., 1993).

In some studies, tumor location seems an important feature for AC, with associations stronger for tumors located more distally (Ji et al., 1997). Associations have remained after adjustment for important confounding factors, such as cigarette smoking and diet (Brown et al., 1995; Chow et al., 1998; Wu et al., 2001).

Most studies show stronger associations for AE than for AC (Figure 22–2); risk estimates are inconsistent and range from the null to sixfold or greater with BMIs of 27 or higher. The study by Lagergren et al. (1999) revealed that associations were stronger for AE (OR = 7.6; 95% CI, 3.8–15.2) than for AC (OR = 2.3; 95% CI, 1.5–3.6) among people with a BMI of more than 30, the odds ratio was 16.2 for AE (95% CI, 6.3–41.4). In some instances, the reported BMI level at which a risk is observed is modest. For example, in one study of AE in British women, a sixfold increased risk was observed for a BMI higher than 22.7 (Cheng et al., 2000). In the study by Chow et al. (1998), a three- to fourfold increase in risk of AE and a twofold increase in risk of AC was observed with a BMI of about 27.5 or greater. Limited data support a dose-response effect, with higher BMIs resulting in higher risk. Wu et al. (2001) observed a significant dose-response, with risk increasing as BMI increased during all periods of adult life (i.e., for BMI at ages 20, 40, and recent adult BMI). Weight gain of 46 pounds or more was shown to be as important a predictor as weight itself (Ji et al., 1997; Chow et al., 1998).

Body size at young age and 20 years before diagnosis also appear to be important contributors to risk (Ji et al., 1997; Lagergren et al., 1999). In some studies, the risk estimates observed for body size at younger ages are larger than those for recent body size. In the study of British women reported by Cheng et al. (2000) BMI at age 20 years appeared to be an important contributor to risk. In addition, associations have been reported as stronger for nonsmokers than smokers, and for younger people (<59) than older people, and as similar for those with and without gastroesophageal reflux disease, for men and women, and for various levels of education (Lagergren et al., 1999; Tretli et al., 1999).

Biological Mechanisms

The underlying biological mechanisms for the association between BMI and AE/AC are not clear. Although it has been proposed that the mechanism involves esophageal reflux, limited data show that the risk
associated with BMI is the same for those with and without symptomatic reflux disease (Lagergren et al., 1999). Other hypotheses for obesity potentially increasing risk include effects of diabetes or insulin-related mechanisms (Cheng et al., 2000), and the delay in esophageal motility associated with obesity (Li and Mobarhan, 2000).

**RENAL CELL CANCER**

**Summary of Findings**

Data from case-control and cohort studies provide convincing evidence of a consistent association of increased risk of renal cell cancer from overweight and obesity that is greater in women than in men. Estimates from a meta-analysis that calculated risks for men and women combined suggest this increase in risk corresponds to a 36% increase for an overweight person and an 84% increase for an obese person (Bergström et al., 2001).

**Epidemiology**

Risk for renal cell cancer is increased in heavier men and women in virtually all studies (Wynder et al., 1974; McLaughlin et al., 1984, 1992; Goodman et al., 1986; Yu et al., 1986; Asal et al., 1988; Kadamini et al., 1989; Maclure and Willett, 1990; Partanen et al., 1991; McCredie and Stewart, 1992; Benhamou et al., 1993; Finkle et al., 1993; Kreiger et al., 1993; Hiatt et al., 1994; Lindblad et al., 1994; Mellemgaard et al., 1994, 1995; Muscat et al., 1995; Chow et al., 1996, 2000; Boeing et al., 1997; Yuan et al., 1998). The one exception is a hospital-based case-control study (Talamini et al., 1990) (Figures 22-3a and 22-3b). In contrast, no association between body size and tumors of the renal pelvis has been demonstrated (McCredie and Stewart, 1992; Chow et al., 2000). Most studies demonstrate a linear dose-response relationship between body weight or BMI and renal cell cancer. However, the increase in relative risk appears to be higher for women than for men, perhaps best demonstrated in the largest multicenter study that included men and women (Mellemgaard et al., 1995). In that study, the relative risk for women in the top quartile of BMI was 2.2 compared to a risk of 1.2 for men in the top quartile of BMI. A similar pattern was observed in the very obese group, with higher increases in risk observed for women compared with men. For very obese women with a BMI in the top 5% (≥38.1), risk was markedly increased to 3.6. In contrast, for a similar group of very obese men, risk was 1.6. In a meta-analysis including 11 studies, risk of incident renal cell cancer was increased by 6% and 7% for each unit increase in BMI for men and women, respectively (Bergström et al., 2001). This increase in risk corresponds to a 36% increase in risk for an overweight person and an 84% increase for an obese person.

Data are limited on adult weight gain and renal cell cancer, and they have not been reported except for three studies. In a 1995 multicenter study, Mellemgaard et al. (1995) examined the slope and variability (coefficient of variation) of BMI, two measures that investigators have conceptualized as representing the rate of weight gain and frequency of weight fluctuations, respectively. In this study, the rate of weight change appeared to be an independent predictor of risk for women but not for men, though the coefficient of variation of BMI was not associated with renal cell cancer after adjustment for BMI in women. One other study, by Chow et al. (2000), examined the association of change in BMI over a period of 6 years and renal cell cancer risk in men and found a non-statistically significant increased risk of 1.6 with an increase in BMI of 2.5 units. Additionally, Bergström et al. (2001) observed that weight gain, especially among subjects with high BMI at age 20 (OR = 1.9, C.I., 1.2–3.0), was associated with an increased renal cell cancer risk.

A number of other factors, including hypertension, diabetes mellitus, and tobacco use, have been consistently associated with risk of renal cell cancer. Each of these factors is related to obesity: Obesity is positively and causally related to hypertension and diabetes mellitus, and tobacco use is associated with leanness. A limited number of studies of obesity and renal cell cancer have adjusted for hypertension and/or smoking (Kreiger et al., 1993; Benhamou et al., 1993; Mellemgaard et al., 1994; Muscat et al., 1995; Chow et al., 1996,
2000). However, none has fully explored potential interactions among these factors. Limited data suggest that risk from obesity is higher among heavier men and women with hypertension (Muscat et al., 1995) and who are nonsmokers (Chow et al., 2000). A limited number of studies have found amphetamines, used in the treatment of obesity and other conditions, to be positively associated with renal cell cancer (Wolk et al., 1996).

**Biological Mechanisms**

The precise mechanisms by which higher body mass might influence renal cell carcinogenesis are not clearly defined. Hormonal factors, particularly sex steroids, have been found to promote renal cell proliferation and growth by direct endocrine receptor-mediated effects (Ronchi et al., 1984), by regulation of receptor concentrations (Traish et al., 1987), or through paracrine growth factors (Concolino et al., 1989). In a 1996 review on nutrition and renal cell cancer, Wolk et al. (1996) also proposed the hypothesis that the metabolic syndrome associated with upper body obesity, including hypertension, glucose intolerance, increased levels of insulin-like growth factor (IGF), and in women, anovulation and increased androgen production, might result in renal damage that would increase the susceptibility of the kidney to other carcinogens.

**ENDOMETRIAL CANCER**

**Summary of Findings**

Data from case-control and cohort studies provide convincing evidence of a consistent association of increased risk of endometrial...
cancer from overweight and obesity with a doubling to tripling of risk observed among obese women. The lifetime risk of being diagnosed with endometrial cancer in the United States is about 3%, whereas the cumulative risk increases to 9% to 10% in obese women (Schottenfeld, 1995). Based on the prevalence of obesity (Flegal et al., 2002) and estimates of relative risk in U.S. women, excessive weight and a central pattern of fat distribution may account for 17% to 46% of endometrial cancer incidence in postmenopausal women. Data suggest that obesity may account for about 40% of the worldwide variation in cumulative rates of endometrial cancer (IARC, 2002). Meta-analyses that provide a more quantitative statement of the association across several studies have not been published.

Epidemiology

Adenocarcinoma of the endometrium is the most common cancer of the female reproductive organs. International variation in endometrial cancer rates may represent differences in the distribution of known risk factors, which include obesity, hormone replacement therapy (HRT), ovarian dysfunction, diabetes mellitus, infertility, nulliparity, and tamoxifen use (Purdie et al., 2001). Comparisons of cumulative rates (ages 0–84) of endometrial cancer with reported data on the prevalence of obesity among women in developed and developing countries suggest that obesity may account for about 40% of the worldwide variation in cumulative rates of endometrial cancer (Akhmedkhanov et al., 2001). Thus, a substantial portion of the international variation in the incidence of endometrial cancer could be explained by differences in the prevalence of obesity.

A consistent positive association between obesity and endometrial cancer risk has been observed in most cohort studies focusing on this association (Ewertz et al., 1984; Folsom et al., 1989, Tretli and Magnus, 1990; Le Marchand et al., 1991; Möller et al., 1994; Törnberg and Carstensen, 1994; Terry et al., 1999; Jain et al., 2000; Furberg and Thune, 2003). Excess risk persists even after adjustment for several factors, such as parity, HRT, and smoking (Le Marchand et al., 1991; Jain et al., 2000). Both Le Marchand et al. (1991) and Törnberg and Carstensen (1994) observed a stronger association between body mass index and endometrial cancer risk with increasing age than have others (Furberg and Thune, 2003). In a study of 47,003 women who were older than 55 years at entry and followed for 25 years, Törnberg and Carstensen (1994) observed a threefold increased risk (RR = 3.16; P < 0.0001) when comparing heavy to lean women (BMI ≥28 vs. BMI > 22).

Consistent with the observation from cohort studies, most case-control studies (Blitzer et al., 1976; La Vecchia et al., 1984, 1991, Lapidus et al., 1988; Austin et al., 1991; Shu et al., 1991; Brinton et al., 1992; Levi et al., 1992; Shu et al., 1992; Swanson et al., 1993; Inoue et al., 1994; Olson et al., 1995; Baanders-van Hakewijn et al., 1996; Kalandidh et al., 1996; Shoff and Newcomb et al., 1998) except three (Koumantaki et al., 1989; Parslov et al., 2000; Beard et al., 2000) observed that women with a BMI of 25 or higher have a two- to threefold increase in risk (Figure 22-4). High BMI was associated with an even greater excess risk in a study in Hawaii that included Japanese, Caucasian, native Hawaiian, Filipino, and Chinese populations (Goodman et al., 1997). Compared to lean women (BMI < 21.1), overweight women (BMI > 27.3) had a fourfold increased risk (RR = 4.3, P < 0.0001). Another large, informative Swedish case-control study with 709 endometrial cancer cases found an even larger increased risk of endometrial cancer with increasing weight (Weiderpass et al., 2000). Compared to lean women (BMI < 22.5), obese women (BMI of 30–33.99) had a threefold increased risk (OR = 2.9, CI, 2.0–4.0), and markedly obese women (BMI > 34) a sixfold increased risk (OR = 6.3, CI, 4.2–9.5). The effect of BMI did not vary by age, menopause, or use of contraceptives. Thus, a linear increase in risk with increasing BMI has been observed.

Weight gain during adulthood is especially interesting, and studies show a linear dose-response relationship between weight gain and endometrial cancer (Le Marchand et al., 1991; Shu et al., 1992; Swanson et al., 1993; Olson et al., 1995; Terry et al., 1999). Two of these studies did not adjust for young adult weight or BMI (Swanson et al., 1993; Olson et al., 1995). The studies that adjusted for young adult or baseline weight or BMI found differing results. In two studies

Cohort Studies: Population-Based

- Ewertz et al. (1984), Denmark, n=115
- Tretli & Magnus (1990), Norway, n=2,208
- Le Marchand et al. (1991), USA, n=214
- Möller et al. (1994), Denmark, n=114
- Terry et al. (1999), Sweden, n=133
- Jain et al. (2000), Canada, n=271

Case-Control Studies: Hospital-Based

- La Vecchia et al. (1984), Italy, Premenopausal, n=283
- La Vecchia et al. (1984), Italy, Postmenopausal, n=283
- Koumantaki et al. (1989), Greece, n=83
- Austin et al. (1991), USA, n=168
- Inoue et al. (1994), Japan, n=143

Case-Control Studies: Population-Based

- Casagrande et al. (1979), USA, n=110
- Shu et al. (1991), China, n=268
- Brinton et al. (1993), USA, n=405
- Swanson et al. (1993), USA, n=405
- Olson et al. (1995), USA, n=222
- Shoff & Newcomb (1998), USA, n=723
- Weiderpass et al. (2000), Sweden, n=709 (RR=6.3)
- Beard et al. (2000), USA, n=117
- Xu (2002), China, n=497

Figure 22-4. Summary of risk estimates and confidence intervals from epidemiologic studies of BMI and endometrial cancer.
that adjusted for either adolescent or early adult weight or BMI, the association between adult weight gain and endometrial cancer remained after adjustment (Le Marchand et al., 1991; Xu et al., 2002). In one other study, adjustment for baseline weight eliminated the association between adult weight gain and endometrial cancer (Terry et al., 1999). In one study in Shanghai, weight loss from ages 20 to 30 was inversely associated with endometrial cancer risk (Xu et al., 2002).

The distribution of body fat, including such measures as skinfold (subscapular) and WHR, also has been examined in several studies (Folsom et al., 1989; Elliott et al., 1990; Austin, 1991; Schapira et al., 1991; Shu et al., 1992; Swanson et al., 1993). Evidence suggests that fat distribution may be important in endometrial cancer, with upper-body obesity particularly increasing risk. A case-control study from Shanghai found that the distribution of subscapular skinfolds was a better predictor for endometrial cancer risk than WHR, even after adjustment for BMI (Shu et al., 1992).

Interaction between obesity and physical activity has been proposed as one explanation for the observation that some studies have observed a stronger positive association between obesity and endometrial cancer risk in older than younger women (Le Marchand et al., 1991; Törnberg and Carstensen, 1994). This finding is consistent with some population evidence that older women are less active than younger women (IARC, 2002). Recently, the established link between diabetes and endometrial cancer risk suggests that hyperglycemia (Furberg and Thuene, 2003) and hyperinsulinemia (Weiderpass et al., 2000; Anderson et al., 2001) may influence risk.

### Biological Mechanisms

Changes in metabolism and hormonal activity that occur in obesity may be important mechanisms that explain the biologically plausible link between increased endometrial cancer risk and obesity. The normal menstrual cycle reflects the complex balance between the proliferative actions of estrogen and the antiestrogenic and secretory transforming actions of progesterone on the endometrium (Hale et al., 2002). A shift to a positive energy balance might contribute to an unfavorable sex hormone profile in women (Key et al., 2001; Jasienska et al., 2001).

Among premenopausal women, obesity may induce a progesterone deficiency during the luteal phase as a result of anovulatory cycles, amenorrhea, and irregular menstrual periods. This situation may lead to an increased proliferation and decreased desquamation of endometrial cells. Among postmenopausal women, several lines of evidence suggest that obesity is associated with increased lifetime exposure to estrogen that may also increase risk: increased aromatization of androgens (androstenedione) to estrone in adipose tissue (Key and Pike, 1988a; Zeleniuch-Jacquotte, 2001), increased secretion of androstenedione in adrenal glands, and decreased sex hormone binding globulin (SHBG), resulting in an increase in bioavailable estradiol (free and albumin bound). Therefore, through different mechanisms for pre- and postmenopausal women, obesity alters sex steroid concentration and metabolism in ways that increase endometrial cancer risk.

Experimental and epidemiological evidence suggest that insulin-like growth factor-1 (IGF-1), a hormone with strong mitogenic and antiapoptotic actions, may be important in endometrial carcinogenesis. A high BMI may alter IGF-1 blood levels, although this has not been examined in studies of endometrial cancer risk. In addition, energy restriction is known to enhance DNA repair, moderate oxidative damage to DNA, and reduce oncogene expression (Lipman et al., 1989).

Another possible biological mechanism is related to the established link between diabetes and endometrial cancer (Furberg and Thuene, 2003) and the fact that obesity is associated with insulin resistance, hyperinsulinemia, and diabetes mellitus. Evidence is increasing that insulin is a growth factor for tumor formation (Yu and Rohan, 2000). The mechanisms underlying insulin-mediated neoplasia may include enhanced DNA synthesis with resultant tumor cell growth, inhibition of apoptosis, and an altered sex hormone milieu. Hence, in overweight and obese women, coexisting metabolic disturbances may act synergistically to facilitate malignant transformation of glandular endometrial cells.
between BMI and premenopausal breast cancer, with a relative risk of 0.54 for women with a BMI higher than 31 compared with women with a BMI of less than 21 (van den Brandt et al., 2000). This estimate is consistent with the reduction in risk of 0.6 to 0.7 observed in many studies and does not appear to be present for BMIs less than 28. An extensive literature on breast cancer prognosis and survival suggests that women who are heavier at the time of diagnosis and gain weight following diagnosis experience a worse prognosis irrespective of menopausal status at diagnosis.

**Epidemiology**

Animal model research in the 1930s first examined the hypothesis that a positive energy balance increased risk for breast cancer (Tannenbaum, 1940a, 1940b). The epidemiological evidence on weight or BMI and breast cancer risk varies by menopausal status (Figures 22-6a and 22-6b), age at diagnosis, hormone receptor status of the breast cancer, and exposure to exogenous estrogens. Because studies of breast cancer have used so many different BMI cutpoints that are not consistent with current WHO criteria of overweight and obese, the following review uses the term heavier women to describe the upper BMI groups rather than the terms overweight and obese. The most informative studies have distinguished between pre- and postmenopausal breast cancer; examined the effect of weight, weight gain, and central body fat at various ages; and have examined the differential effects of endogenous and exogenous estrogens. With the emergence of a possible IGF-mediated pathway for several cancers, recent studies have also begun to explore the potential interactions of IGF with body size.

Most studies find that heavier women have a decreased risk of premenopausal breast cancer (Paffenbarger et al., 1980; Willett et al., 1985; Hislop et al., 1986; Le Marchand et al., 1988a; London et al., 1989; Swanson et al., 1989; Trentham-Dietz et al., 1997; Chie et al., 1998; Galanis et al., 1998; Magnusson et al., 1998; Enger et al., 2000; Hall et al., 2000; Lam et al., 2000; Li et al., 2000; Trentham-Dietz et al., 2000; Shu et al., 2001; Yoo et al., 2001; Friedenreich et al., 2002). Other studies find no association between BMI and premenopausal breast cancer (Hirose et al., 2001; Shu et al., 2001; Yoo et al., 2001). Relative risks of approximately 0.6 to 0.7 have been reported whether weight or BMI is assessed at the time of diagnosis or at earlier times during childhood, adolescence, or adulthood (Hislop et al., 1986; Kolonel et al., 1986; London et al., 1989; Brinton et al., 1992). Early studies suggested that the protective effect among heavier women was limited to early-stage disease due to poorer detection of small tumors (Willett et al., 1985; Swanson et al., 1989). However, subsequent studies in these same groups suggest that detection bias does not explain the increased risk for breast cancer observed among lean premenopausal women (London et al., 1989; Brinton et al., 1992; Swanson et al., 1996). A large case-control study of 1588 cases 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). A meta-analysis of seven cohorts comprising 723 incident cases of invasive breast cancer in premenopausal women found an inverse association between BMI and premenopausal breast cancer; the relative risk was 0.54 for women with a BMI higher than 31 compared to women with a BMI less than 21 (van den Brandt et al., 2000). This estimate is consistent with the reduction in risk of 0.6 to 0.7 observed in many studies and does not appear to be present for BMIs less than 28.

Conversely, most studies have found that heavier women are at increased risk of postmenopausal breast cancer (Valaoras et al., 1969; de Waard et al., 1974; Choi et al., 1978; Paffenberger et al., 1980; Kalish, 1984; Lubin et al., 1985; Hislop et al., 1986; Kolonel et al., 1986; Le Marchand et al., 1988a; Negri et al., 1988; Tao et al., 1988; Ingram et al., 1989; Tretli et al., 1989; Folsom et al., 1990; Hseih et al., 1990; Parazzini et al., 1990; Chu et al., 1991; Harris et al., 1992; Pathak et al., 1992; Sellers et al., 1992, 2002; Radimer et al., 1993; Francheschini et al., 1996; Yong et al., 1996; Ziegler et al., 1996; Trentham-Dietz et al., 1997; Chie et al., 1998; Galanis et al., 1998; Magnusson et al., 1998; Enger et al., 2000; Hall et al., 2000; Lam et al., 2000; Li et al., 2000; Trentham-Dietz et al., 2000; Shu et al., 2001; Yoo et al., 2001; Friedenreich et al., 2002; Wenten et al., 2002; Lahmann et al., 2003). A meta-analysis of seven cohorts comprising 3208 cases of invasive postmenopausal breast cancer found gradual increases in risk to a BMI of 28 after which risk did not increase further; the relative risk for a BMI of 28 compared with a BMI of less than 21 was 1.26 (van den Brandt et al., 2000). The majority of studies on BMI and breast cancer risk have adjusted for major breast cancer risk factors, including reproductive factors. Few studies have examined in detail the effect of confounding or interactions with diet and...
Cohort Studies: Hospital-Based
Yoo et al. (2001), Japan, n=1,154

Cohort Studies: Population-Based
Le Marchand et al. (1988a), USA, age 30-49, n=148
Le Marchand et al. (1988b), USA, age 45-49, n=141
Tretli (1989), Norway, n=5,122
Vatlen & Kvinnsland (1992), Norway, n=291
Huang et al. (1997), USA, n=1,000
Manjer et al. (2001), Sweden, n=3,112
Van Den Brandt et al. (2001), Pooled analysis of 8 studies, n=3,208

Case-Control Studies: Hospital-Based
Hsieh et al. (1990), International, n=3,993
Kolonel et al. (1999), USA, n=1,016
Chen et al. (1999), Taiwan, n=324
de Vasconcelos et al. (2001), Brazil, n=177
Hirose et al. (2001), Japan, n=65

Case-Control Studies: Population-Based
Hislop et al. (1986), Canada, n=306
Chu et al. (1991), USA, n=2,053
Brinton & Swanson (1992), USA, n=414
Swanson et al. (1996), USA, n=1,588
Yong et al. (1998), USA, n=226
Jiang et al. (1996), USA, n=421
Coste et al. (1999), USA, n=1,590
Pocock et al. (1999), USA, n=484
Engel et al. (2000), USA, n=400
Hall et al. (2000), USA, Black, n=389
Hall et al. (2000), USA, White, n=389
Shu et al. (2001), China, n=1,459
Friedenreich et al. (2002), Canada, n=462

Cohort Studies: Hospital-Based
Yoo et al. (2001), Japan, n=1,154

Cohort Studies: Population-Based
Le Marchand et al. (1988a), USA, age 50-54, n=145
Le Marchand et al. (1988b), USA, age 55-65, n=135
Tredl (1989), Norway, n=8,122
Sellers et al. (1992), USA, n=1,000
Sellers et al. (1992), USA, n=1,074
Huang et al. (1997), USA, n=1,517
Manjer et al. (2001), Sweden, n=312
Sellers et al. (2002), USA, n=1,074
Sellers et al. (2002), USA, n=1,874
Lahmann et al. (2003), Sweden, n=246
Van Den Brandt et al. (2001), Pooled analysis of 8 studies, n=3,208

Case-Control Studies: Hospital-Based
Hsieh et al. (1990), International, n=3,993
Kolonel et al. (1999), USA, n=1,016
Franceschi et al. (1999), Italy, n=988
Che et al. (1998), Taiwan, n=334
Lam et al. (2000), USA, n=529
de Vasconcelos et al. (2001), Brazil, n=177
Hirose et al. (2001), Japan, n=44

Case-Control Studies: Population-Based
Hislop et al. (1986), Canada, n=306
Chu et al. (1991), USA, n=2,053
Brinton & Swanson (1992), USA, n=414
Swanson et al. (1996), USA, n=1,588
Yong et al. (1998), USA, n=226
Jiang et al. (1996), USA, n=421
Coste et al. (1999), USA, n=1,590
Pocock et al. (1999), USA, n=484
Engel et al. (2000), USA, n=400
Hall et al. (2000), USA, Black, n=389
Hall et al. (2000), USA, White, n=389
Shu et al. (2001), China, n=1,459
Friedenreich et al. (2002), Canada, n=462

Figure 22-6. A, Summary of risk estimates and confidence intervals from epidemiologic studies of BMI and breast cancer in premenopausal women (limited to studies with at least 100 cases). B, Summary of risk estimates and confidence intervals from epidemiologic studies of BMI and breast cancer in postmenopausal women (limited to studies with at least 100 cases).
physical activity. Only one study in Vermont that had data on breast density from screening mammograms controlled for the effect of breast density (Lam et al., 2000). Because BMI is inversely related to breast density, adjustment for breast density resulted in an increase in the risk estimations at all levels of BMI; the OR increased from 1.9 to 2.5 after adjustment for breast density among obese women.

When examined, risk estimates for the association between obesity and breast cancer vary by age at diagnosis, history of HRT, estrogen receptor status of the tumor, and possibly family history of breast cancer. Risk has been found to increase with age at diagnosis in some studies that include a substantial number of postmenopausal women older than 65 years (Yong et al., 1996; van den Brandt et al., 2000; Friedenreich et al., 2002). In one study, risk estimates increased from 1.1 among women younger than 60 years to 1.8 among women older than 65 years (Yong et al., 1996).

The effect of exogenous estrogen or estrogen receptor status of tumors has been examined with stratified analyses in more recent studies. In these studies, obesity-related risk has been higher among women who have never used HRT (Huang et al., 1997; Lam et al., 2000; Friedenreich et al., 2002; Lahmann et al., 2003). One of the largest cohort studies in the United States found a statistically significant BMI and estrogen replacement interaction, with no increase in risk (RR of 1.1) among all women but an increase in risk (RR of 1.6) among heavier women who had not used HRT (Huang et al., 1997). At least three studies have examined risk by BMI and estrogen receptor status of the breast tumor (Enger et al., 2000; Yoo et al., 2001; Sellers et al., 2002). In one U.S. study, risk for a BMI of 27 compared with a BMI of 22 was 2.4 for tumors that were both estrogen and progesterone receptor positive (Enger et al., 2000). In another study, risk estimates were 2.0 and 2.2 for a BMI of 30.7 compared with a BMI of 23 for estrogen receptor positive and progesterone positive tumors, respectively (Sellers et al., 2002). In both of these studies, obesity-related risk was not increased for estrogen or progesterone receptor negative tumors. In a Japanese study, risk did not vary by estrogen or progesterone status of the tumor (Yoo et al., 2001). However, the women in this study were lean; the upper quartile of BMI of 22 in this study is lower than the lowest quartile of BMI in most U.S. studies.

Data are very limited on variation in BMI-related risk for postmenopausal breast cancer by family history. In several studies from the Iowa Women’s Health Study, heavier postmenopausal women with a family history of breast cancer have a greater risk of developing breast cancer than do heavier women without a family history (Sellers et al., 1992; Sellers et al., 2002). In one study in Japan, no differences were observed in associations of weight, BMI, or change in BMI by family history for premenopausal breast cancer, although somewhat stronger associations were seen for weight and change in BMI and postmenopausal breast cancer among postmenopausal women with a family history of breast cancer, confirming earlier results by Sellers and colleagues (Hirose et al., 2001). Only one study has examined variation in BMI-related risk for premenopausal breast cancer by family history of breast cancer (Swedlow et al., 2002). In that study, the inverse association commonly observed between BMI and breast cancer risk was only observed in women without a family history of breast cancer.

Weight or BMI at birth, during childhood, and early in adulthood have been examined relative to breast cancer. The data on birth weight and breast cancer are limited by a very small number of cases, with most studies having fewer than 100 cases. Some studies find no association (Le Marchand et al., 1988b; Ekbom et al., 1997), or a non-significant increased risk (Hilakivi-Clarke et al., 2001); others find an increase in risk with increasing birth weight for premenopausal but not postmenopausal breast cancer (Berstein, 1988; Ekbom et al., 1992; Michels et al., 1996; Sanderson et al., 1996; Innes et al., 2000) or a stronger increase in risk for premenopausal compared to postmenopausal breast cancer (De Stavola et al., 2000; Kaijser et al., 2001). In most studies, heavier weight or BMI during teenage and young adulthood (18–20 years) is associated with a 10% to 30% decrease in breast cancer risk for both pre- and postmenopausal breast cancer. This decreased risk is most often not statistically significant (Paffenbarger et al., 1980; Willett et al., 1985; London et al., 1989; Folsom et al., 1990; Lund et al., 1990; Chu et al., 1991; Brinton and Swanson, 1992; Sellers et al., 1992; Ursin et al., 1995; Huang et al., 1997; Magnusson et al., 1998; Coates et al., 1999; Peacock et al., 1999; Enger et al., 2000; Hirose et al., 2001; de Vasconcelos et al., 2001; Wenten et al., 2002). During the middle decades of life, the risk associated with BMI remains inverse for premenopausal breast cancer and increases with age for postmenopausal breast cancer.

Increases in central adiposity have been associated with a 1.4- to 2.0-fold increase in breast cancer risk among postmenopausal women in most studies (Ballard-Barbash et al., 1990a; Folsom et al., 1990; Schairer et al., 1990; Bruning et al., 1992a, 1992b; Sellers et al., 1992; Ng, 1997; Shu et al., 2001; Friedenreich et al., 2002). However, not all studies show this association (den Tonkelaar et al., 1992; Petrek, 1993; Lahmann et al., 2003). Data on central adiposity and premenopausal breast cancer do not suggest a consistent association between measures, such as waist circumference or WHR, and breast cancer risk (Franchesci et al., 1996; Mannisto et al., 1996; Swanson et al., 1996; Ng et al., 1997; Kaaks et al., 1998; Huang et al., 1999; Sonnenschein et al., 1999; Hall et al., 2000; Shu et al., 2001; Friedenreich et al., 2002). Only five of these studies observed statistically significant increases in risk (Mannisto et al., 1996; Ng et al., 1997; Sonnenschein et al., 1999; Hall et al., 2000; Shu et al., 2001). The association in postmenopausal women may be modified by a family history of breast cancer and ovarian cancer. In the Iowa Women’s Health Study, among women with elevated WHR, only women with a positive family history of breast cancer were at increased risk. The combination of a high WHR with a family history of breast and ovarian cancer was associated with a more than fourfold increase in risk of breast cancer (Folsom et al., 1990; Sellers et al., 1993).

The most consistent body size predictor of postmenopausal breast cancer risk is adult weight gain (Lubin, 1985; Le Marchand et al., 1988b; Ballard-Barbash, 1990b; Folsom et al., 1990; Brinton et al., 1992; Radimer et al., 1993; Barnes-Josiah et al., 1995; Ziegler et al., 1996; Huang et al., 1997; Magnusson et al., 1998; Jernström and Barrett-Connor, 1999; Enger et al., 2000; Li et al., 2000; Trentham-Dietz et al., 2000; Shoff et al., 2000; Hirose et al., 2001; Shu et al., 2001; Friedenreich et al., 2002; Wenten et al., 2002; Lahmann et al., 2003). This association has been seen in cohort studies that found no association between BMI at baseline and subsequent development of breast cancer and that also adjusted 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 postmenopausal breast cancer was associated with a weight gain of more than 20 kg after the age of 18 years, but only among women who had never used postmenopausal HRT (Huang et al., 1997). Other studies have observed similar results, with increases in risk either limited to or much larger among women who have gained more weight and who have never used HRT compared to current users (Harris et al., 1992; Magnusson et al., 1998; Trentham-Dietz et al., 2000; Friedenreich et al., 2002; Lahmann et al., 2003). Consistent with findings for BMI and premenopausal breast cancer, weight gain appears to be associated with a reduced or no significant increased risk of premenopausal breast cancer in most studies (Le Marchand et al., 1988a; London et al., 1989; Brinton et al., 1992; Huang et al., 1997; Coates et al., 1999; Peacock et al., 1999; Hirose et al., 2001; Shu et al., 2001; de Vasconcelos et al., 2001; Friedenreich et al., 2002; Wenten et al., 2002). However, a study by Wenten et al. (2002) in New Mexico found differences in risk for Hispanic compared to non-Hispanic white women. In that study, no association was found between weight gain and risk of premenopausal breast cancer among non-Hispanic white women; in contrast, a non-statistically significant but nearly twofold increased risk was observed with more than 14 kg of weight gain among Hispanic white women.

The only study that has examined the effect of percent body fat measured by bioelectric impedance as well as several other measures of body size, fat mass, and distribution found the strongest association for percent body fat, with a doubling of risk for women with a percent body fat of over 36% compared to women with a percent body fat of less than 27%. Similar to results reported for BMI and weight gain, risk for percent body fat was stronger among women who had
Breast Cancer Prognosis

Extensive data indicate that heavier women experience 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; Verrault et al., 1989; Coates et al., 1990; Tretli et al., 1990; Kyogoku et al., 1990; Vatten et al., 1991; Senie et al., 1992; Giuffrida et al., 1992; Bastarachea et al., 1994; Zhang et al., 1995; den Tonkelaar et al., 1995; Maehle and Tretli, 1996). The effect of weight or BMI on prognosis appears to be limited to or more pronounced among women with stage I and II disease (Verrault et al., 1989; Tretli and Magnus, 1990), estrogen receptor and progesterone receptor positive status (Coates et al., 1990; Giuffrida et al., 1992; Maehle and Tretli, 1996), and negative nodes (Mohle-Boetani et al., 1988; Newman et al., 1997). The most precise risk estimates for BMI and breast cancer prognosis are derived from large population-based cohorts of breast cancer cases. In the largest cohort of more than 8000 women with breast cancer, risk varied by stage at diagnosis (Tretli and Magnus, 1990). 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 IV disease (Tretli and Magnus, 1990). In a subset of 1238 women from this cohort who had unilateral breast cancer treated with modified radical mastectomy and were followed for 15 years, the risk of dying from breast cancer relative to BMI varied markedly by hormone receptor status (Maehle and Tretli, 1996). Although women with estrogen receptor and progesterone receptor positive tumors had a 46% reduced risk of dying from breast cancer, the risk within hormone receptor positive and negative groups varied by BMI. Among women with hormone receptor positive tumors, obese women had a threefold higher risk of death than did thin women. Conversely, among women with hormone receptor negative tumors, thin women had a sixfold higher risk of death than did obese women, even after adjustment for lymph node status, tumor diameter, and mean nuclear area. One study that examined the association of BMI with distant recurrence and death found a 70% to 80% increase in risk of both distant recurrence and death among women with a BMI of 27.8 or greater (Goodwin et al., 2002a). This study also examined the association of fasting insulin, IGF, and estradiol to these outcomes and found increased risk of distant recurrence and death among women with elevated insulin, but not with elevated IGF-1, IGF-II, and estradiol. A subsequent study in this same sample found that the binding proteins of IGFBP-1 and IGFBP-3 were inversely associated with risk of distant recurrence, but only IGFBP-1 was also inversely associated with risk of death (Goodwin et al., 2002b).

Weight gain is reported in the majority of women undergoing adjuvant therapy for breast cancer (Heasman et al., 1985; Goodwin et al., 1988, 1999; Camoriano et al., 1990; Demark-Wahnefried, 1993). Weight gain associated with treatment is lowest among women not receiving systemic therapy, intermediate among women receiving hormonal therapy, and more pronounced among women receiving adjuvant chemotherapy and those who undergo menopause after diagnosis and treatment. To identify optimal interventions to prevent weight gain during treatment, research has begun to examine whether changes in energy intake and expenditure during and after treatment are associated with weight gain (Demark-Wahnefried et al., 1993, 2001; De Waard et al., 1993). Although data on the association of post-diagnosis weight gain and prognosis are limited, the largest study of 646 premenopausal women found that women who gained more than 5.9 kg were 1.5 times as likely to relapse and 1.6 times more likely to die than women who gained less weight (Camoriano et al., 1990).

Biological Mechanisms

Ovarian Hormone Metabolism

The major focus of research on mechanisms underlying body size and breast and endometrial cancer risk has been the effects of adiposity on endogenous hormonal, predominantly estrogen, metabolism; this research has been extensively reviewed (Kirschner et al., 1981; Key and Pike, 1988b; Bernstein and Ross, 1993; Key et al., 2001). Hypotheses have evolved from a focus on estrogen excess, to the combined effects of estrogen and progesterone, and most recently, to attempts to delineate factors defining bioavailability and effects of estrogens and androgens and their metabolites on specific end organs. Increases in overall and central adiposity have been associated with increases in insulin, androgens, and triglycerides; decreases in SHBG; and increases in total and free estradiol (Evans et al., 1984; Haffner et al., 1989; Kirschner et al., 1990; Kaye et al., 1991; Bruning et al., 1992a, 1992b; Potsichman et al., 1996). A number of these hormonal changes increase the bioavailability of estradiol and its metabolites and may also directly promote tumor growth.

The bioavailability of estradiol is dependent on the degree of binding and the strength of binding to several protein carriers. SHBG is the predominant protein carrier of estradiol and the percentage of free estradiol is generally inversely related to the level of SHBG. However, estradiol is also transported and bound, though less tightly, to albumin. Increases in free fatty acids, such as triglycerides, has been reported to increase the level of free estradiol by displacing estradiol from SHBG where it is tightly bound, to albumin, where it is less tightly bound. Therefore, both decreases in SHBG and increases in triglycerides may result in increases in free estradiol.

Key and Pike (1988a, 1988b) first proposed that the effect of adiposity on the bioavailability of estrogen was modulated by menopausal changes in estrogen and progesterone production, and so explained the apparent contradictory findings for premenopausal and postmenopausal breast cancer. Before menopause, ovarian estrogen production overwhelms changes in estrogen metabolism related to the overall level of adiposity. Consequently, estradiol in ovulatory cycles does not differ measurably in obese compared to lean women. In contrast, estradiol levels are reduced in anovulatory cycles that are more frequent in obese than lean premenopausal women. Conversely, obese premenopausal women have been found to have markedly reduced progesterone levels, both due to increased frequency of anovulation and decreased progesterone production in the luteal phase. With the onset of menopause, the decreased risk associated with premenopausal obesity declines over time. In postmenopausal women, the overall level of adiposity results in increases in estrogenic activity by increases in estrogen production from androgens (Kirschner et al., 1981), decreased estrogen-protein binding (Bruning, 1987) due to decreases in SHBG (Moore et al., 1987; Kaye et al., 1991; Bruning et al., 1992b) and increases in triglycerides (Bruning et al., 1992b). Furthermore, the C-2 hydroxy metabolite of estrogen has been proposed to be a less tumorogenic metabolite of estrogen, and C-2 versus 16-hydroxylation of estradiol is reported to be decreased in obese women (Schneider et al., 1983). A well-designed study using contemporary, high-quality assays for sex steroids found that the increases in estrone, estradiol, free estradiol, and albumin-bound estradiol associated with increases in BMI were not present in premenopausal women but were statistically significant among postmenopausal women (Potsichman et al., 1996).

Insulin, Insulin-like Growth Factors, and Other Hormones

Insulin, insulin-like growth factors, and binding proteins (BPs) may promote hormone-dependent tumors through direct effects on tumor cells (Foeckens et al., 1989; Yee et al., 1989; Turner et al., 1997), and through indirect effects on estrogens and possible interactions with estrogen at the estrogen receptor on breast cancer cells (Clayton et al., 1997; El-Tanani et al., 1997). A comprehensive review of epidemiological research by Yu and Rohan (2000) summarized the mitogenic and antiapoptotic actions of IGFs on various cancer cells, their synergistic effects with other growth factors and steroids, and the associations of IGFs and binding proteins with cancer. The research on
breast cancer is briefly reviewed here. Five of seven studies that have examined the effect of IGF-I have found an increased risk of premenopausal breast cancer associated with increased IGF-I (Peyrat et al., 1993; Bruning et al., 1995; Del Giudice et al., 1998; Hankinson et al., 1998; Toniole et al., 2000). However, only one of these studies (Bruning et al., 1995) found a statistically significant increased risk. Three studies found no association between IGF-I and postmenopausal breast cancer (Bruning et al., 1995; Hankinson et al., 1998; Jernström and Barrett-Connor, 1999), and one study found a difference in mean IGF-I in cases and controls (Agurs-Collins et al., 2000). C-peptide, a marker of hyperinsulinemia, has been associated with breast cancer risk in two studies (Bruning et al., 1992a; Yang et al., 2001). One study that observed an increase risk of postmenopausal breast cancer with weight gain did not find that this increased risk was explained by levels of IGF-I, fasting insulin, proinsulin, or C-peptide (Jernström and Barrett-Connor, 1999). Few other studies have examined whether insulin, IGF, or related growth factors might explain part of the increased risk associated with BMI, weight gain, or central body fat. Data on the association between IGF-I and BMI or fat mass are mixed (Yu and Rohan, 2000), with some studies finding no association (Kelly et al., 1990; Landin-Wilhelmsen et al., 1994; Goodman-Gruen et al., 1997; Janssen et al., 1998; Kaklamani et al., 1999), some an inverse association (Colletti et al., 1991; Veldhuis et al., 1995; Marin et al., 1993; Maccarino et al., 1999), and some, particularly in lower BMI ranges, a positive association (IARC, 2002). However, IGF-I is hypothesized to be associated with the degree of muscle mass, and is related to the preservation of muscle mass in animal studies. Studies have not examined whether increases in muscle mass also may explain the increased premenopausal breast cancer risk observed among tall and lean women.

Other Hormonal Hypotheses

Animal studies have examined the effect of various other hormonal measures, such as growth hormone, cortisol, on breast cancer development. These factors may vary by body weight, fat mass, or body fat distribution, but studies in humans have not examined these as potential mechanisms for weight-related breast cancer risk. One study has examined the association of leptin, a hormone that reflects total fat mass, with premenopausal breast cancer and found a non-significant lower level of leptin in cases compared to controls (Mantzoros et al., 1999). This finding is consistent with the inverse association between BMI and premenopausal breast cancer. No published studies have examined associations of leptin with postmenopausal breast cancer. Circulating leptin is closely related to insulin levels and adiposity. It increases the amount of adipose tissue in the body (Bennett et al., 1997; Niskanen et al., 1997) by regulating food intake and energy balance (Larsson et al., 1998; van Aggel-Leijssen et al., 1999) and interacting with other endocrine systems (Licino et al., 1997; Haffner et al., 1997). Insulin increases leptin gene expression, stimulates leptin protein production in rodents, and regulates leptin and SHBG protein levels in vivo and in vitro (Segal et al., 1996; Johannsson et al., 1998; Russell et al., 1998; Ho et al., 1999).

Other Mechanisms

With the recent emergence of studies suggesting that physical activity may reduce risk of breast cancer, a limited number of analyses have examined the possibility of effect modification or interaction between physical activity and various weight-related measures (Thune et al., 1997). Although some studies have included physical activity in a large list of covariates within multivariate models to adjust for confounding, no analyses have reported whether effect modification by physical activity is observed in risk estimates for weight-related measures and breast cancer. Similarly, although diet has been proposed as a major mediator of the association of weight or BMI with postmenopausal breast cancer risk, no analyses have been designed to examine this issue. The large error in self-reporting of energy, greater in heavier compared to lighter individuals (Heitman, 1999; Heitman et al., 2003), limits the ability to examine this issue with currently available data.

PROSTATE CANCER

Summary of Findings

Extensive data from cohort and case-control studies provide convincing evidence of no association between body mass index and prostate cancer. Data on other anthropometric measures, such as abdominal obesity, muscle mass, or weight gain, are too limited to allow for any definitive conclusion.

Epidemiology

The association of BMI and incidence of prostate cancer has been examined in 33 studies conducted worldwide. Of these, 13 are cohort studies (Figure 22-7) (Nomura et al., 1985; Severson et al., 1988; Mills et al., 1989; Chyou et al., 1994; Le Marchand et al., 1994; Thune and Lund, 1994; Andersson et al., 1997; Cerhan et al., 1997; Giovannucci et al., 1997; Lund Nilsen and Vatten, 1999; Clarke and Whittemore, 2000; Habel et al., 2000; Putnam et al., 2000; Schuurman et al., 2000; Lee et al., 2001). The remaining 20 are case-control studies (Wynder et al., 1971; Graham et al., 1983; Talamini et al., 1986; Ross et al., 1987; Kolonel et al., 1988; Yu et al., 1988; Mettlin et al., 1989; West et al., 1991; Andersson et al., 1995; Whittemore et al., 1995; Andersson et al., 1996; Grönborg et al., 1996; Ilic et al., 1996; Key et al., 1997; Demark-Wahnefried et al., 1997a; Hayes et al., 1999; Hsieh et al., 1999; Villeneuve et al., 1999; Bairati et al., 2000; Hsing et al., 2000; Spitz et al., 2000; Sharpe and Siemiatycki, 2001). Of these 33 incidence studies, seven observed an increased prostate cancer risk among men who were in the highest category of BMI (Thune and Lund, 1994; Grönborg et al., 1996; Andersson et al., 1997; Key et al., 1997; Putnam et al., 2000; Spitz et al., 2000) or weight (Chyou et al., 1994) as compared to those in the lowest category. In these seven studies, the increased risk was small, 10% on average, across these categories of BMI, and the range in risk estimates was from 0.5 to 4.4. The remaining studies found no association between obesity and increased prostate cancer risk.

Most epidemiological studies of obesity and prostate cancer have used BMI as a measure of obesity. However, the ranges for BMI used in these studies have not been standardized. Residual confounding that might have concealed weak associations with anthropometry is a possibility in these studies, particularly because several did not have a full examination of all possible confounding factors. Nonetheless, given the large number of studies conducted, the consistency of the results, the low magnitude of the association, and the limited evidence of a dose-response effect, the lack of association between body mass index and prostate cancer is convincing.

In addition to examining BMI, several of these investigations evaluated the possible associations of weight with prostate cancer risk. Consistently, no associations were found for increased risk with weight. It is possible, however, that other anthropometric measures may be more strongly associated with prostate cancer risk. Body mass index measures both lean body mass and adiposity. Other anthropometric measures of body fat distribution may be more strongly related to prostate cancer risk because this cancer is androgen-dependent, and lean body mass is related to androgen levels. Fewer studies have examined lean body mass or abdominal adiposity, thereby limiting any conclusive assessments of the associations. Severson et al. (1988) found an increased prostate cancer risk in a Japanese population associated with the area of muscle in the arm and not with the fat in the arm. A Norwegian cohort study found no increased risk with lean body mass (Lund Nilsen and Vatten, 1999). Similarly, an American study found no association with lean body mass or fat mass area as measured in the arm (Clarke and Whittemore, 2000).

Weight gain throughout the lifetime and increased abdominal adiposity also are possible prostate cancer risk factors, although few studies have evaluated these variables. Schuurman et al. (2000) found a significant positive trend for increasing quintiles of BMI at age 20, but no increased risk for high weight gain from age 20 to time of interview. Hsing et al. (2000) found that abdominal adiposity, as measured by WHR, increased prostate cancer risk in Chinese men. The observed increased risk with WHR was independent of BMI, socioeconomic factors, and age.
Incidence Studies: Cohort Studies

- N=174: Inodence Studies, Cohort Studies by Nunn et al. (1985), Severson et al. (1988), USA
- N=198: Severson et al. (1989), USA
- N=306: Taylor et al. (1990), USA
- N=180: Marchand et al. (1994), USA
- N=220: Lewine & Lund (1994), Norway
- N=198: Moller et al. (1994), Denmark
- N=1,369: Taroni et al. (1997), USA
- N=71: Rothern et al. (1997), USA
- N=2,368: Andersson et al. (1997), Sweden
- N=220: Undem & Vatten (1999), Norway
- N=302: Pusum et al. (2000), USA
- N=642: Schuurman et al. (2000), Netherlands
- N=642: Havel et al. (2000), USA
- N=439: Lee et al. (2001), USA

Case-Control Studies: Hospital-Based

- N=166: Talaini et al. (1986), Italy
- N=1,162: Yu et al. (1988), USA
- N=371: Menlin et al. (1989), USA
- N=156: Demark-Wahnefried et al. (1997a), USA
- N=103: Stepe et al. (2000), USA
- N=64: Jairari et al. (2000), Canada

Case-Control Studies: Population-Based

- N=256: Andersson et al. (1995), Sweden
- N=256: Andersson et al. (1996), Sweden
- N=406: Gronberg et al. (1996), Sweden
- N=328: Ley et al. (1997), United Kingdom
- N=449: Hayes et al. (1999), USA, Blacks
- N=483: Hayes et al. (1999), USA, Whites
- N=1,623: Volleneuve et al. (1999), Canada
- N=239: Hsing et al. (2000), China
- N=399: Sharpe and Siemiarycki (2001), Canada

Case-Control Studies (2000hf)

- N=256: Andersson et al. (1995), Sweden
- N=256: Andersson et al. (1996), Sweden
- N=406: Gronberg et al. (1996), Sweden
- N=328: Ley et al. (1997), United Kingdom
- N=449: Hayes et al. (1999), USA, Blacks
- N=483: Hayes et al. (1999), USA, Whites
- N=1,623: Volleneuve et al. (1999), Canada
- N=239: Hsing et al. (2000), China
- N=399: Sharpe and Siemiarycki (2001), Canada

Biological Mechanisms

Prostate cancer is a hormone-mediated cancer in that endogenous hormones regulate the growth and function of the prostate gland (Henderson et al., 1982). Administration of large quantities of testosterone can induce prostate cancer in rodents (Noble, 1977). Men who have high estrogen levels rarely develop prostate cancer (Glantz, 1964). A Western lifestyle, characterized by a positive energy balance, has consistently been implicated as a risk factor for prostate cancer in international comparisons and experimental studies (Hebert et al., 1998; Bosland et al., 1999; Mukherjee et al., 1999). The evidence, however, from individual-level epidemiologic studies on the associations between dietary intake, obesity, and physical activity and prostate cancer risk is weaker (Friedenreich and Thune, 2001; Schulman et al., 2001). Despite the lack of an association between BMI and prostate cancer from epidemiologic studies, several studies of biological markers that are related to obesity suggest an association of these markers with prostate cancer.

Leptin, an adipocyte-derived hormone that regulates satiety and energy expenditure, has been shown to increase prostate cancer risk. It is suggested as a key link between a state of continual positive energy balance and the transition from premalignant lesions to overt prostate cancer (Stattem, 2001). In addition, higher serum insulin...
levels increase prostate cancer risk independent of abdominal adiposity (Hsing et al., 2001). Despite these associations, it is unclear whether the concomitant hormonal and metabolic changes that occur because of abdominal adiposity and insulin resistance are the biological mechanisms for the link between insulin and prostate cancer risk.

Two other biomarkers for prostate cancer risk that may be related to BMI and either fat or muscle mass have been identified from studies in diverse populations: IGF-I (Mantzoros et al., 1997; Chan et al., 1998; Wolk et al., 1998) and serum testosterone (Shanyefyel et al., 2000). A meta-analysis of published studies on hormonal predictors of prostate cancer risk found that men with serum testosterone or IGF-I levels in the upper quartile of the population distribution have an approximately twofold higher prostate cancer risk (Shanyefyel et al., 2000). Levels of dihydrotestosterone and estradiol were not found to have as strong an association with prostate cancer risk (Shanyefyel et al., 2000). Overall, exposure to endogenous androgenic hormones appears to be positively associated with prostate cancer risk (Bosland, 2000). A number of studies have explored the associations between various sex steroids and BMI in men (Glass, 1989; Kato et al., 1992; Andersson et al., 1997; Demark-Wahnefried et al., 1997b; Tymchuk et al., 1998; Tamani et al., 2001; Sarma et al., 2002). However, how BMI may play a role in the association of these measures with prostate cancer is complex and not well understood.

THYROID CANCER

Summary of Findings

Data from case-control and cohort studies are suggestive of an increased risk of thyroid cancer among heavier individuals (BMI cutpoints not defined) that is present only for women. Estimates from a meta-analysis suggest a 20% increase in risk in women (Dal Maso et al., 2000).

Epidemiology

A meta-analysis (Dal Maso et al., 2000) summarized and reanalyzed evidence from the existing case-control studies on obesity and thyroid cancer (McTiernan et al., 1984; Preston-Martin et al., 1987; Ron et al., 1987; Linos et al., 1989; Kolonel et al., 1990; Francheschi et al., 1991; Levi et al., 1991; Goodman et al., 1992; Glattre et al., 1993; Preston-Martin et al., 1993; Wingren et al., 1993; Hallquist et al., 1994; D’Avanzo et al., 1995; Galanti et al., 1997; Negri et al., 1999). The authors reported that relative risk for the upper tertile of BMI at the time of diagnosis was above unity for 9 of the 12 studies in women, with a relative risk overall for the highest compared to the lowest tertile of 1.2 (95% CI, 1.0–1.4), P for trend of 0.04. The overall relative risk for the highest compared to the lowest tertile in men was 1.0, with a nonsignificant P for trend.

Similarly, in five case-control studies that have examined this factor, no association has been observed for thyroid cancer risk and BMI between the ages of 17 to 20 (McTiernan et al., 1984; Preston-Martin et al., 1987; Linos et al., 1989; Preston-Martin et al., 1993; Wingren et al., 1993). One case-control study of papillary thyroid cancer in women (Rossing et al., 2000), published after the Dal Maso (2000) meta-analysis, found that women who weighed 158 pounds or more had a 1.5-fold increased risk. Another case-control study in women found no association between BMI and thyroid cancer (Mack et al., 2002) but did observe a non-statistically significant increase in risk with weight gain. The only cohort study to examine the association between obesity and thyroid cancer risk found no statistically significant association with BMI at the baseline interview or with weight gain since age 20 (Iribarren et al., 2001).

Biological Mechanisms

Several mechanisms have been proposed for the modest association observed in many case-control studies in women. Most relate to potential interactions between thyroid hormones and other steroid hor-
Head and Neck Cancers

Although tobacco and alcohol use account for more than 90% of cancers of the head and neck in developing countries (IARC, 1986, 1988), leanness also has been associated with increased risk of head and neck cancers in some case-control studies. No cohort studies examining this association have been published. Six case-control studies found an inverse association between weight and/or BMI and cancer of the oral cavity and pharynx (McLaughlin et al., 1988; Marshall et al., 1992; Day et al., 1993; Kabat et al., 1994; D'Avanzo et al., 1996; Francheschii et al., 2001) and one found a non-statistically significant risk estimate of 1.5 among heavier women (Negri et al., 2000). Two other studies found weaker inverse associations between BMI and laryngeal cancer (Muscat and Wynder, 1992; D'Avanzo et al., 1996). Similar to findings for lung cancer, several studies found either no association (Kabat et al., 1994; Francheschii et al., 2001) or weaker associations (D'Avanzo et al., 1996) between BMI and oral cancer among never smokers compared to current smokers. These results suggest that BMI is not causally related to risk of head and neck cancers. However, similar to lung cancer, the causal factors contributing to head and neck cancer among never smokers may be different than those among current or former smokers.

CANCER SITES WITH INSUFFICIENT EVIDENCE FOR CONCLUSIONS

Limited epidemiologic evidence exists on weight or BMI for a number of other cancers, including leukemia, non-Hodgkin lymphoma, malignant melanoma, and testicular, pancreatic, bladder, and cervical cancers. However, data for these and other cancer sites are too limited to allow specific conclusions to be made and are not summarized here due to space limitations. A summary of the evidence for several of these other cancer sites is provided in the February 2002 IARC publication Weight Control and Physical Activity (IARC, 2002).

DATA ON CANCER MORTALITY

Because of space limitations and the difficulty of disentangling the effect of screening and treatment from individual-based risk factors, such as obesity, when examining cancer mortality as an outcome, this review does not provide a detailed overview of the evidence on obesity and cancer mortality. However, a recent study from a large U.S.-based cohort provides several new insights (Calle et al., 2003). In this study, the effect of obesity on cancer mortality was examined in a cohort of more than 900,000 adults who developed more than 57,000 cancers in 16 years of follow-up. The study is unique in that it provided estimates for multiple cancers within one cohort and one report and had a much larger sample size than any other single report to date. Therefore, the study was able to provide estimates for multiple cancers, including more precise estimates for less common cancers, and examined the effect of overweight and obesity among nonsmokers. The study found that BMI was associated with higher rates of death in both men and women for cancers of the esophagus, colon and rectum, liver, gallbladder, pancreas, kidney, non-Hodgkin lymphoma, and multiple myeloma. BMI was also associated with higher rates of death from cancers of the stomach and prostate in men and cancers of the breast, uterus, cervix, and ovary in women. Based on rates of overweight and obesity present in the United States in 1999 to 2000, the study estimated that 14% of cancer deaths in men and 20% of cancer deaths in women could be attributed to overweight and obesity.

FUTURE DIRECTIONS

Studies are needed that have sufficient power and complete data on a number of factors to adequately control for all confounders of the association between BMI and cancer, and to study subgroups postulated to be at very low or high risk. In addition, more studies on weight and height at an early age in life with a long follow-up are needed to clarify the role of weight and weight gain throughout the life span. For some cancer sites, a number of studies corrected only for age, thus allowing uncontrolled confounding to influence the results. Important confounders to consider include physical activity, other anthropometric factors such as height, smoking status, dietary intake, and other lifestyle factors. A full examination of all anthropometric risk factors and cancer is also needed. For some cancer sites, such as breast cancer, additional measures such as body fat distribution, weight gain, and body composition have been examined. However, for most cancer sites, very few studies have considered any factor other than BMI. Moreover, studies that examine a full range of possible effect modifiers need to be conducted because relatively few investigations have examined risks within subgroups of the population defined on characteristics such as ethnic origin/race, other lifestyle risk factors (e.g., physical activity, dietary intake, smoking status), HRT, genetic factors (e.g., family history of cancer or other comorbid diseases, such as diabetes that may influence the health consequences of obesity), or other possible risk factors, such as breast density in the case of breast cancer. Studies that provide data specific to racial and ethnic groups are increasingly important. At present, most of the data on obesity and cancer are based on population samples drawn from Europe, the United States, Canada, Australia, Japan, and China, and therefore have largely included whites of European descent, Chinese, Japanese, and Hawaiians. Data are very limited for African-American men and women or those of North, Central, or South American Latina descent or for many populations in Asia and Africa. In addition, data on these groups are seldom reported separately even within large case-control or cohort studies that may include these populations.

To clarify the extent to which anthropometric factors are risk factors for specific cancers, further research is needed to delineate the role of site-specific biological mechanisms, particularly for endogenous hormones, insulin, insulin-related growth factors, leptin, cortisol, and related hormones that may influence the development of body fat, skeletal structure, and musculature and that may underlie observed associations with cancer outcomes. Evidence is evolving rapidly about genetic factors that may have particular importance in the metabolism of sex steroids and insulin or in the development of obesity. Future studies are needed to examine how specific genes predict underlying metabolic profiles and subsequent cancer risk.

An overview of the potential biological mechanisms that have been either hypothesized or examined as possible explanations for the association of obesity with specific cancers is presented in Table 22-1. This overview demonstrates that many of these cancers are hypothesized to be hormone based, either in terms of sex steroids or, more recently, in terms of insulin, leptin, or insulin-related growth factors. Although not explored to any extent in humans, research in animal models suggest that factors such as cortisol or vitamin D may also explain some of the risk associated with obesity. Using animal models, these mechanisms have largely been explored by studies of caloric restriction rather than by studies of increases in energy expenditure (Hurting et al., 2003).

Two other areas of emerging research should be briefly noted. With improved detection and treatment, many people are living longer and healthier lives with cancer, and therefore, studies on the effect of obesity on cancer prognosis are needed. At present, research in prognosis has been largely limited to breast cancer and should be extended to other cancers. In addition, to achieve a better understanding of what interventions may reduce risk, studies of the effect of specific dietary and exercise programs to control weight are needed, particularly studies that can elucidate the effect of such interventions on underlying mechanisms that may influence carcinogenesis.

EXTENT OF THE OBESITY EPIDEMIC AND MANAGEMENT STRATEGIES

The WHO 2000 report Obesity: Preventing and Managing the Global Epidemic is the most recent comprehensive source summarizing the
global epidemic of obesity. Within that report, the WHO MONICA study provides a full spectrum of data comparing rates of obesity worldwide for the period 1983–1986. At that time, the international prevalence of obesity, defined as a BMI of 30 and higher, ranged from 5% to 20% for men and 10% to 40% in women (WHO, 2000). The WHO 2000 report highlighted several major features of the international patterns of body weight and associated health outcomes. For the first time, more people were classified as experiencing obesity than were suffering from starvation in developing as well as developed countries. The report also noted the rapidly increasing rates of obesity in some Asian countries, such as Japan and China, where the prevalence of obesity traditionally had been very low. Similar to patterns observed in the United States, rates of obesity in other countries are generally higher among women than men and in urban as compared to rural communities. Although data on children are more limited, evidence suggests that obesity is also increasing in children worldwide in developed and developing countries. In 2000, the WHO initiated a global strategy for preventing and controlling non-communicable diseases that includes a focus on combatting the worldwide rise in obesity through reducing unhealthy diets and physical inactivity.

The United States, the prevalence of obesity has changed dramatically over the past 40 years. It was relatively stable at approximately 10% for men and 15% for women during the early 1960s to the late 1970s. During the late 1980s and early 1990s rates of obesity increased, and the most current estimates from the 1999–2000 National Health and Nutrition Examination Survey (NHANES) indicate that the prevalence of obesity has increased to 27.5% for men and 33.4% for women (Flegal et al., 2002). Rates tend to increase with age to about age 70; at later ages, they decline slightly. Rates are highest among non-Hispanic black women who experience a 50% prevalence of obesity.

When the prevalence of overweight, or a BMI of 25 and higher, is considered, about 65% of the U.S. adult population is affected. Of particular concern are increases in rates of overweight among children and adolescents. Prevalence rates, which were approximately 5% during the 1960s, have tripled to over 15% in 1999–2000 among school-aged children and adolescents. Rates rose by 10 percentage points or more between 1988 and 1994 and between 1999 and 2000 for both Mexican American and non-Hispanic black adolescents (Ogden et al., 2002).

Estimating the consequences and cost of obesity internationally is complex because obesity and overweight are risk factors for multiple chronic diseases other than cancer, including non–insulin-dependent diabetes mellitus, insulin resistance, gallbladder disease, hyperlipidemia, coronary heart disease, hypertension, osteoarthritis, sleep apnea, low-back pain, polycystic ovarian disease, impaired fertility, reproductive hormone abnormalities, surgical complications, and anesthesia complications. International estimates of the economic cost have ranged from 2% to about 7% of national health care costs, with the United States reporting the highest cost of 7% (WHO, 2000). In 1990, this cost was estimated to be $45.8 billion dollars from the direct cost of obesity-associated diseases and $23.3 billion from lost productivity (Wolf and Colditz, 1994). In an updated analysis, Wolf and Colditz (1998) estimated the total U.S. direct cost attributable to obesity to be $99.2 billion, which represented 5.7% of the total U.S. national health expenditure that year.

A comprehensive overview of the treatment and prevention of obesity is beyond the scope of this review. These issues are addressed in detail in the WHO 2000 report Obesity: Preventing and Managing the Global Epidemic and other reviews (Kopelman, 2000). Advances in the field of obesity, particularly in terms of the genetics of obesity and its implication for developing more targeted and effective treatment approaches, have been highlighted in issues of Science (February 2003) and Nature (April 2000). Preventing and controlling obesity requires comprehensive societal efforts and must target lifelong health habits at the individual level. In addition, continued research is needed to find better means of identifying individuals at risk of developing obesity and its adverse consequences because of their genetic, familial, or other environmental risk factors. At present, with the rapid increase in obesity in developed and developing countries among all age groups, including children, prevention has become an urgent worldwide priority. Issues of particular concern in cancer control include the need to develop better strategies to facilitate the avoidance of weight gain during adult life and to identify whether specific interventions during treatment can alleviate treatment-related weight gain that has been identified to worsen breast cancer prognosis, but may also be an issue for other cancers. Key public health recommendations and strategies relevant to cancer are reviewed in the 2002 IARC report on Weight Control and Physical Activity (IARC, 2002).

### CONCLUSIONS AND POPULATION ATTRIBUTABLE RISK

At present, data provide convincing evidence of a positive association of overweight and obesity with cancers of the colon (among men), renal cell, postmenopausal breast, endometrium, and probable evidence of a positive association with colon cancer (among women),
Potential for marked increases in the PAR for obesity and weight-obesity in women is 33\%, the PAR for endometrial cancer is 33\%. The European Union. In contrast, in the United States, whose rate of 22\% when the prevalence of obesity was 13\% for women within the European Union published by Bergström and colleagues (2000) was 3\%. The PAR estimate for obesity and endometrial cancer within the European Union as estimated by Bergström and colleagues (2000) and rates of less than 3\% the PAR for a cancer with a twofold increase due to obesity, such as endometrial cancer, is less than 0.26\%, 37\%, and 39\%, respectively. However, these estimates were based on international rates of overweight and obesity from the 1990s (IARC, 2002) and are higher in the United States today given the continued increase in the prevalence of overweight and obesity. Table 22-2 provides a comparison of PARs for five major weight-related cancers for the European Union (EU) from 1982 to 1996 and the United States from 1999 to 2000.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overweight</td>
<td>Obese</td>
</tr>
<tr>
<td>Colon</td>
<td>6.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Renal</td>
<td>15.2</td>
<td>10.3</td>
</tr>
<tr>
<td>Endometrium</td>
<td>17.2</td>
<td>22.0</td>
</tr>
<tr>
<td>Breast (postmenopausal)</td>
<td>4.1</td>
<td>4.5</td>
</tr>
<tr>
<td>USA</td>
<td>9.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Colon</td>
<td>19.4</td>
<td>19.0</td>
</tr>
<tr>
<td>Kidney</td>
<td>26.8</td>
<td>33.4</td>
</tr>
<tr>
<td>Endometrium</td>
<td>6.9</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Overweight/obesity prevalence rates used: EU overweight and obesity rates were, respectively, 35\% and 19\% for men, and 50\% and 13\% for women. For the United States from 1999 to 2000, the rates were increased to 67\% and 28\% for men and 62\% and 33\% for women.

*Source of RR and EU PARs is Bergström et al. (2000).

Epidemiologic studies do not demonstrate an association of weight or BMI with prostate cancer incidence. In addition, limited evidence does not suggest any consistent direct association between overweight or obesity and ovarian cancer. The consistent inverse association between overweight or obesity and lung, and head and neck, cancers is reduced with adjustment for tobacco use; therefore, overweight and obesity are not considered to be protective for these cancers. The inverse association between overweight and obesity and premenopausal breast cancer persists after adjustment for multiple potential confounding factors. Extensive data provide convincing evidence of a positive association between obesity and endometrial cancer and adverse changes in breast cancer prognosis and mortality.

Estimates of the population attributable risk (PAR) of cancer due to overweight and obesity have been summarized in the 2002 IARC report and are modest for some cancers, such as colon and post-menopausal breast cancer. Approximately 9\% to 11\% of these cancers are attributable to overweight or obesity. PAR estimates are more substantial for renal cell, esophageal, and endometrial cancer: 25\%, 37\%, and 39\%, respectively. However, these estimates were based on international rates of overweight and obesity from the 1990s (IARC, 2002) and are higher in the United States today given the continued increase in the prevalence of overweight and obesity. Table 22-2 provides a comparison of PARs for five major weight-related cancers for the European Union as estimated by Bergström and colleagues (2000) and for the United States based on rates of obesity and overweight from the 1999–2000 NHANES survey. The PARs estimated by Bergström and colleagues (2001) were based on relative risk estimates from meta-analyses and from rates of obesity in European Union countries from 1982 to 1996. Because of increases in rates of overweight and obesity in the United States, PARs are higher for the United States than those estimated for the European Union. Figure 22–8 shows the potential for substantial increases in PARs with increases in rates of overweight/obesity and relative risk estimates of overweight/obesity with cancer. For example, in a country such as Japan, which has obesity rates of less than 3\%, the PAR for a cancer with a twofold increase due to obesity, such as endometrial cancer, is less than 3\%. The PAR estimate for obesity and endometrial cancer within the European Union published by Bergström and colleagues (2000) was 22\% when the prevalence of obesity was 13\% for women within the European Union. In contrast, in the United States, whose rate of obesity in women is 33\%, the PAR for endometrial cancer is 33\%. The potential for marked increases in the PAR for obesity and weight-related cancers is further demonstrated in Figure 22–9, which demonstrates the relatively strong association between rates of obesity and endometrial cancer prevalence internationally. Similar associations can be seen for other cancers as well. With the expectation that the epidemic of obesity is likely to continue, if not accelerate, in the near term, overweight and obesity will become increasingly important contributors to cancer risk internationally.

Acknowledgments

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Table 22–2. Population Attributable Rates (PAR in %) for Weight-Related Cancers for the European Union (EU) from 1982 to 1996 and the United States from 1999 to 2000

<table>
<thead>
<tr>
<th>Cancer</th>
<th>EU*</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overweight</td>
<td>Obese</td>
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<tr>
<td>Colon</td>
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</tr>
<tr>
<td>Endometrium</td>
<td>17.2</td>
<td>22.0</td>
</tr>
<tr>
<td>Breast (postmenopausal)</td>
<td>4.1</td>
<td>4.5</td>
</tr>
<tr>
<td>USA</td>
<td>9.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Colon</td>
<td>19.4</td>
<td>19.0</td>
</tr>
<tr>
<td>Kidney</td>
<td>26.8</td>
<td>33.4</td>
</tr>
<tr>
<td>Endometrium</td>
<td>6.9</td>
<td>7.6</td>
</tr>
</tbody>
</table>

*Source of RR and EU PARs is Bergström et al. (2000).

The data show a significant association between obesity and endometrial cancer. The figure illustrates the potential for marked increases in the PAR for obesity and weight-obesity in the European Union compared to the United States.
References


Obesity and Body Composition


PART III: THE CAUSES OF CANCER


