Obesity as a Risk Factor for Certain Types of Cancer[1]

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A survey of body weight, smoking, and cancer mortality involving 750,000 Americans over the period from 1959 to 1972 showed a 33% increase in cancer deaths for men and a 55% increase for women whose body weight was more than 40% above average. Overweight men had significantly higher rates of colorectal cancer, whereas women had higher rates of cancers of the breast, cervix, endometrium, gallbladder and biliary passages, ovary, and uterus (1). It should be noted, however, that being overweight is not necessarily synonymous with obesity (2).

Other more recent studies, such as the Danish record-linkage study (3), have provided additional evidence of an association between obesity and cancer (4–6). This is a matter for concern because of the high incidence of obesity in many countries and because of the increasing incidence of obesity in many parts of the world (5–15).

The aim of this review is to summarize information on obesity in relation to cancer at the various sites for which there is evidence of a positive association.

ENDOMETRIAL CANCER

The link between obesity and endometrial cancer is well-established (4,16–18), particularly for postmenopausal women (19). The association has been observed in both case–control and follow-up studies and in many cases was confined to very obese women (18). The relationship is stronger in older women (19–21). A positive association between endometrial cancer and upper body fat, as measured by waist-to-hip ratio or waist-to-thigh ratio, has been observed in some studies (22–24), but not in others (25). In some cases, this positive association disappeared after adjustment for body mass index (BMI) (26–28).

The association between obesity and endometrial cancer probably has a hormonal basis. Endometrial epithelial cells are stimulated by elevated estrogen levels; and this stimulation, unopposed by progesterone, is thought to be conducive to development of cancer (29,30). Obese women have higher levels of serum estrone and estradiol (27,28,31), presumably as a result of the production of estrogen in adipose tissue by aromatization of androstenedione (32). Obese women also have decreased levels of sex hormone-binding globulin, thus increasing the amount of bioavailable estrogen (32–34).

Steroid measurements in urine collected from women in a cohort study provided further evidence in favor of the hypothesis that unopposed estrogen is a risk factor for endometrial cancer (35). In a recent case–control study, high circulating levels of androstenedione were associated with increased risk of endometrial cancer in both pre- and postmenopausal women, but high levels of estrone and estradiol were only associated with increased risk in postmenopausal women (36). In premenopausal women, obesity may influence endometrial cancer through its tendency to cause amenorrhea and luteal phase progesterone deficiency (21).

BREAST CANCER

A number of studies have shown that obesity increases the risk of breast cancer in postmenopausal women (4,5,17, 37–43). In contrast, a meta-analysis showed a modest inverse association between BMI and premenopausal breast cancer (44). An inverse association between adiposity and breast cancer has also been observed in a number of other studies (43). This may not apply in all cases, however, since a study of women in seven different countries showed that incidence of breast cancer in premenopausal women increased with body mass in low- and moderate-risk countries but decreased with increasing body mass in high-risk countries. In postmenopausal women, the rates increased with body mass in all risk groups (45,46). Cohort studies have been less supportive of the positive correlation between body mass and breast cancer in postmenopausal women than case–control studies (39,41; but see 42).

Breast cancer may also be influenced by the distribution of body fat. An increase in central adiposity has been reported to increase the risk of postmenopausal breast cancer, independent of relative weight, particularly when there is a family history of breast cancer (41). Breast cancer patients were also found to have more visceral fat compared to subcutaneous fat than controls, as measured by computed tomography (47).

Breast cancer risk was not found to be related to body fat distribution in women under 45 yr of age (48). In agreement with earlier studies, Swanson *et al.* (48) found an inverse correlation between body weight and breast cancer in young

[1]This paper was prepared as one of the background documents for the WHO Consultation on Obesity (Geneva, Switzerland, 3-5 June 1997). For further details, please see the report of the Consultation, Obesity: preventing and managing the global epidemic (WHO/NUT/NCD/97.2).

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Abbreviation: BMI, body mass index.

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women. It was concluded that this probably can not be explained by increased frequency of anovulatory cycles or by detection bias (45).

Adult weight gain has consistently been associated with increased risk of breast cancer, even in cohort studies that showed no association between baseline relative weight and subsequent risk of breast cancer (17,43). In most studies, increased body mass was associated with poorer survival and increased likelihood of recurrence, and adverse outcomes were more pronounced among postmenopausal women and women with less advanced disease (41,49,50). In this connection, it is of interest that most women gain weight during the menopause (51). Weight loss has been associated with reduced risk in some studies but not in others (17,43,52).

Breast cancer, like endometrial cancer, is strongly influenced by hormonal factors, and the differing effects of adiposity on pre- and postmenopausal breast cancer may be explainable on the basis of differences in steroid hormone metabolism (41). Before the menopause, the ovaries are the main source of estrogen, whereas after the menopause production from the ovaries decreases and the estrogen produced in adipose tissue by aromatization of androstenedione assumes greater importance, particularly in obese individuals (53,54). Other factors, such as increased levels of androstenedione and decreased levels of sex hormone-binding globulin, may enhance the risk of breast cancer as well as endometrial cancer after the menopause.

In a recent brief communication, Potischman *et al.* (55) reported that serum total estradiol levels decreased with increasing BMI in premenopausal women, whereas they increased in postmenopausal women. This could be a reason for the differing relationships between obesity and breast cancer in premenopausal compared to postmenopausal women. They suggested that the lower levels of estrogen in obese premenopausal women may be due to uptake by adipocytes and a higher metabolic clearance rate. Gerber (56) suggested, on the other hand, that high estrogen levels may be a cause of leanness in premenopausal women. This idea was based on the observation of an inverse relationship between BMI and high density lipoprotein cholesterol levels in premenopausal women. It was suggested that stimulation of hepatic lipoprotein lipase by estrogen results in high low density lipoprotein cholesterol and lower serum triglycerides, leading to lower BMI.

Breast cancer normally originates in mammary epithelial tissue (57) and the adipose tissue of the mammary gland may have a particularly important influence on the epithelial tissue because of their close association with one another (58). This influence may be exerted through estrogens produced in the adipose tissue or through other fat-soluble compounds, such as eicosanoids formed from polyunsaturated fatty acids present in the lipids of adipose tissue (59). An experiment showed a positive correlation between the fat content of the mammary gland in rats on different diets and the number of mammary tumors induced by 7,12-dimethylbenz(a)anthracene in rats on those diets (60). The possibility that mammary gland mass is positively associated with risk of breast cancer has been discussed by Trichopoulos and Lipman (61).

Hyperinsulinemia related to obesity and insulin resistance may pose a risk for breast cancer (62,63). In a case–control study, serum levels of C-peptide, a marker of hyperinsulinemia, were significantly higher in patients with early breast cancer compared to controls, but the study indicated that hyperinsulinemia with insulin resistance was a risk factor for breast cancer independent of general adiposity or body fat distribution (64).

PROSTATE CANCER

Obesity does not appear to be an important risk factor for prostate cancer (4). Although some cohort studies have shown a positive association with overweight, others have not, nor have most case–control studies (65). In a recent report on a large cohort of Swedish construction workers, various aspects of body size, including adult weight and BMI, were positively associated with prostate cancer, and the risk was more strongly related to mortality than to incidence (66). A high BMI may be due to greater muscle mass rather than adipose tissue, and a prospective study in Japanese-American men showed a positive association between prostate cancer and muscle area, but not fat area (67). In fact, obese men with prostate cancer have been reported to have a better prognosis than those with more normal weight (68). This could be related to inhibition of prostate cancer growth and metastasis by increased endogenous estrogen and decreased endogenous testosterone, associated with obesity.

PANCREATIC CANCER

A positive association between body weight or obesity and pancreatic cancer has been reported in some studies but not others (3,69). It has been suggested that effects of obesity on pancreatic cancer may be mediated through sex hormones, since the pancreas contains sex hormone receptors and the anti-estrogen, tamoxifen, inhibits the growth of pancreatic tumors (69).

COLORECTAL CANCER

Although the relationship of BMI to colon cancer has been investigated rather extensively, there does not appear to be a clear consensus (4,70,71). Obese men have been reported to be at higher risk, whereas obese women are not (5). In contrast, the authors of a recent report on a large cohort study in Denmark concluded that the least obese men had the highest risk of colon cancer (72). In the Framingham study, obesity in men combined with low serum cholesterol was associated with four times greater risk compared to people with average values (73). Other studies indicated that obesity in adolescence or early adulthood poses a risk of colon cancer for men (71,74,75).

A report on Harvard alumni provided evidence that higher

levels of Quetelet's index were associated with higher colon cancer risk only among those who were less active (76). The results of a recent large case–control study by Slattery *et al.* (77) also indicated that a large BMI was more strongly associated with increased risk of colon cancer in individuals who were physically inactive and had a high energy intake. There was some evidence that men may be at higher risk than women, especially older women, as a result of an unfavorable energy balance.

In other recent studies, higher BMI was related to higher risk of adenomas in the distal colon in both men and women (78,79). This relationship was stronger for larger adenomas. It was also observed that waist circumference and waist-to-hip ratio are positively related to higher risk of large colon adenomas or cancer in men (78). Slattery *et al.* (77) reported that those at greatest risk of colon cancer had the most unfavorable energy balance, were physically inactive, had high energy intakes and large BMI.

Insulin is a growth factor for colonic mucosal cells and a mitogen for colonic carcinoma cells *in vitro,* and insulin or related growth factors may mediate the influence of obesity on colon cancer (80). Men have a greater tendency than women to accumulate fat tissue in the abdomen, and this is associated with higher insulin levels, which could help to account for the stronger association between obesity and colon cancer in men (80).

Although cancers of the colon and rectum are frequently considered together as colorectal cancer, the rectum differs from the colon in a number of respects (70). Colon cancer and rectal cancer should therefore probably be considered separately in relation to factors that affect them. In a study of Seventh-Day Adventists, a 25% excess in body weight was associated with increased rectal cancer in both men and women, but with increased colon cancer in men only (81). Whereas BMI was positively correlated with higher risk of colonic adenomas in both men and women, it was not apparently related to rectal adenomas in women (78,79).

RENAL CELL CANCER

Renal cell cancer has been consistently associated with overweight and obesity (4,82). The results of case–control studies and a large multicenter study indicated that body weight has a stronger impact on renal cell cancer in women than on men, and in the multicenter study, rate of weight change appeared to be an independent risk factor for women (82). The stronger association in women suggests a role for increased levels of endogenous estrogens (4). These may affect renal cell proliferation and growth by means of receptors present in renal cells or through paracrine growth factors (82).

CANCER AT OTHER SITES

In the large American study cited in the introduction, obese women had higher rates of cancer at a number of sites other than those discussed above (1). The Danish record-linkage study of obese subjects also showed increased incidence of cancer at some additional sites, including the esophagus, liver, and ovary (3). The excess cancers of the esophagus and liver may have been related to higher alcohol intake in the obese cohort. Obese women tend to have more anovulatory cycles, which might affect their susceptibility to ovarian cancer (3). The risk of epithelial ovarian cancer has been observed to decrease with increasing numbers of full-term pregnancies (83). One of the more surprising observations in the Danish study was an excess of brain cancer in the year following discharge from hospital, for which there was no good explanation (3).

SUMMARY AND CONCLUSIONS

In conclusion, obesity has been associated with increased risk for a number of different types of cancer. The evidence has been most consistent for endometrial cancer, breast cancer in postmenopausal women, and renal cell cancer. More variable results have been reported for colorectal, prostate and pancreatic cancer.

Possible mechanisms by which obesity may influence cancer risk include alteration in hormonal patterns, including sex hormones and insulin, and factors such as the distribution of body fat and changes in adiposity at different ages. The increasing prevalence of obesity in many parts of the world emphasizes the importance of learning more about the relationship between obesity and cancer and the mechanisms involved in their interaction.

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[Received August 26, 1997, and in revised form July 24, 1998; revision accepted October 16, 1998]