

# Obesity and Cancer

Jean Paul Deslypere

Large-scale studies have demonstrated that obesity increases the risk of developing some forms of cancer. The association between obesity and cancer may result from factors such as fat distribution or sex hormone levels. Studies have also shown a relationship between a high-fat, low-fiber diet and cancer risk. High estrogen levels and low progesterone levels are associated with an increased risk of endometrial cancer. Obesity is known to raise estrogen levels and may lower progesterone levels. Obesity may increase the risk of breast cancer, but the evidence is less clear, since factors, such as age, country of origin, body-fat distribution, and family history, also play a major role in determining breast cancer risk. Sex hormones, insulin, and nutritional factors are also involved in the etiology of breast cancer. The incidence of lung cancer is inversely related to body weight.

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## CANCER RISK

A NUMBER of studies have been performed in large groups of patients to assess the long-term effects of obesity on the risk of developing cancer. The American Cancer Society Study<sup>1</sup> included more than 750,000 individuals with a 12-year follow-up period. The study showed that obese men and women have an increased risk of some types of cancer. In obese women, there was an increased risk of cancer of the endometrium, cervix, ovary, and breast. In obese men, the incidence of colorectal and prostate cancer was increased. The Danish Record Linkage Study,<sup>2</sup> which consisted of almost 44,000 individuals and an 11-year follow-up period, found a higher risk of cancer of the esophagus, liver, and pancreas in obese men and women. There was also an increased risk of some endocrine cancers, such as endometrial cancer, and certain gastrointestinal cancers, as well as kidney cancer, in obese women.

These studies have demonstrated a positive correlation between obesity and a number of cancers (Table 1). However, the relationship between obesity and the risk of cancer is not straightforward, as other studies failed to show an increased risk of cancer in obese patients.<sup>3-5</sup>

## RISK FACTORS

Epidemiological data suggest that obesity itself or an associated factor may increase the risk of cancer. For example, age is an important determinant for breast cancer. Premenopausal obese women do not have an increased risk of breast cancer,<sup>2</sup> while obese postmenopausal women are at greater risk than non-obese postmenopausal women.<sup>6</sup> Fat distribution,<sup>7</sup> insulin levels,<sup>8</sup> sex hormone levels,<sup>9</sup> nutrition,<sup>10</sup> and use of diuretics<sup>11</sup> may all affect the risk of cancer. The use of diuretics by obese women may explain the higher incidence of kidney cancer seen in these women in some studies.<sup>12</sup>

Hormones are another important factor that may affect the development of cancer in obese patients. There is a

significant association between high estrogen and low progesterone levels, both of which are often found in obese women, and cancer of the endometrium.<sup>2</sup> Insulin and insulin-related growth factors could play a role in cancer development, but there is no evidence that individuals with high insulin levels, such as people with non-insulin-dependent diabetes mellitus (NIDDM) or Pima Indians, have an increased incidence of cancer.<sup>8</sup>

Nutrition is probably a confounding factor in obesity and cancer. Many studies have linked nutritional factors, such as energy intake, fat intake, saturated fat intake, amount of fiber, vegetable consumption, and alcohol intake, with certain types of cancers, but there are also discordant studies.<sup>10</sup>

## ENDOMETRIAL CANCER

A clear relationship exists between endometrial cancer and obesity. Studies have shown an increased risk of cancer with increasing body mass index (BMI). In one study, the relative risk of endometrial cancer more than doubled in women aged 60 to 69 years with a BMI of 25 to 29 kg/m<sup>2</sup>.<sup>13</sup> The increased risk is possibly due to raised estrogen levels.

A recent study from Sweden<sup>14</sup> has shown that a high saturated fat intake may increase the risk of endometrial cancer in obese patients. The fatty acid profile of abdominal fat is closely correlated with fatty acid intake. Abdominal fat biopsies from women with endometrial cancer contained more saturated fatty acids and fewer polyunsaturated fatty acids than lean control subjects. This suggests that fat intake and composition may affect the risk of cancer.

## BREAST CANCER

The relationship between breast cancer and obesity is not clear, as there are a number of confounding factors. The most significant are age, country of origin, body-fat distribution, and family history. Age has a significant impact on the risk of developing breast cancer. Premenopausal obese women have the same risk of breast cancer as lean women, but postmenopausal obese women are at greater risk of breast cancer than lean women.<sup>15</sup> A second confounding factor is the country of origin.<sup>16</sup> Breast cancer rates increase with increasing BMI among women living in countries with a moderate or a low risk of breast cancer, such as Japan. The relationship between BMI and breast cancer is less clear in countries with a higher risk of breast cancer (Fig 1).

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*From the Department of Endocrinology, Division of Internal Medicine, University Hospital, Pintelaan, Ghent, Belgium.*

*Address reprint requests to Jean Paul Deslypere, MD, PhD, Department of Endocrinology, Internal Medicine, University Hospital, Pintelaan, Ghent, Belgium.*

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**Table 1. American Cancer Society Study: Mortality Ratio (N = 750,000; 12-year follow-up)**

Site	Mortality Ratio	
	120%-129% IBW	> 140% IBW
<b>Men</b>		
Colorectal		1.73
Prostate	1.37	1.29
<b>Women</b>		
Endometrium	1.85	5.42
Cervix	1.51	2.39
Ovary		1.63
Breast		1.63

Abbreviation: IBW, ideal body weight.

Adapted with permission.<sup>1</sup>

Fat distribution can affect the relative risk of breast cancer in obese patients. In some studies, an increased risk of breast cancer is more highly correlated with central adiposity than with BMI.<sup>7</sup> Other studies have reported no relationship between body-fat distribution and the risk of breast cancer; for example, triceps and subscapular skinfold thickness were not related to the relative risk of breast cancer.<sup>17</sup> A recent study measured the amount of visceral and subcutaneous fat using a computed tomography scanning technique. Patients with breast cancer had a significantly greater visceral fat layer and a smaller subcutaneous fat layer than noncancer patients matched for BMI.<sup>18</sup>

Family history is the other important confounding factor

in breast cancer. Centrally obese women with a positive family history of breast cancer have a greater relative risk of breast cancer compared with centrally obese women without a family history of breast cancer.<sup>19</sup>

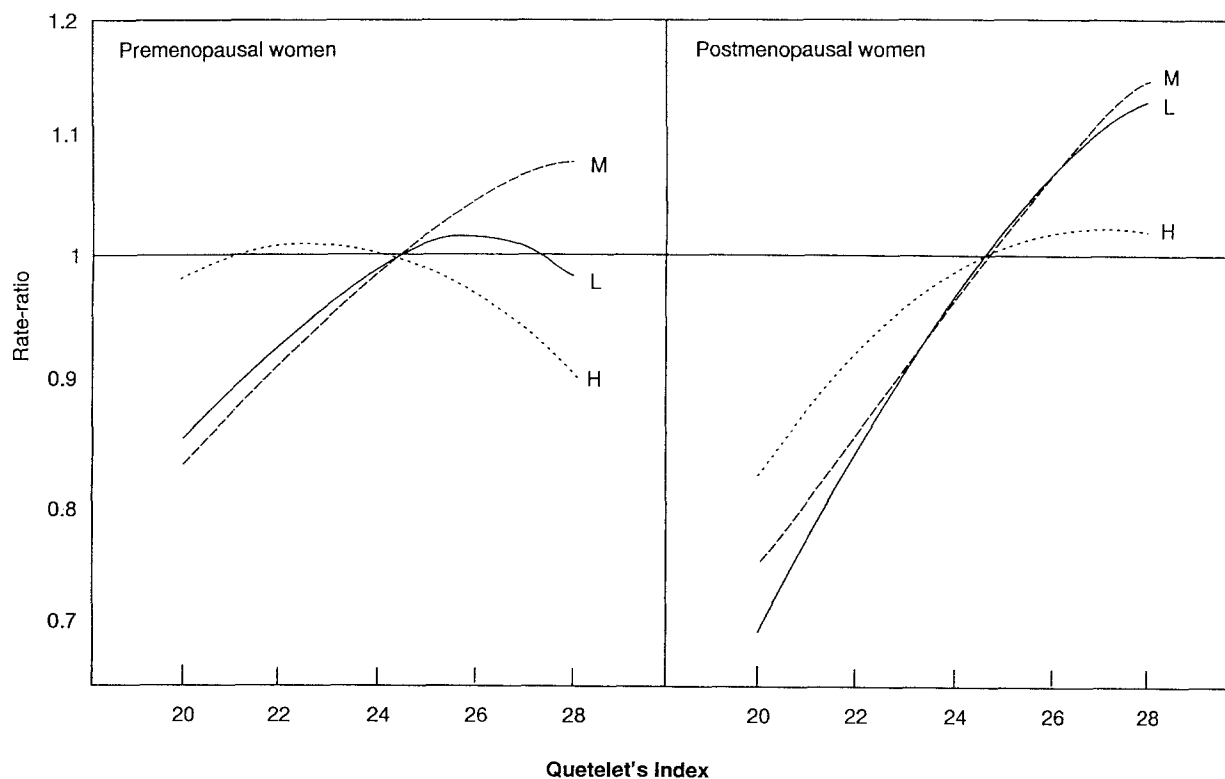
Another factor that could be important in the pathogenesis of breast cancer in obese patients is fat intake.<sup>20</sup> However, most studies have not shown a good correlation between (saturated) fat intake and the risk of this cancer.<sup>21-23</sup>

Studies to date show that obese women who are postmenopausal, live in countries with a moderate risk of breast cancer, have significant abdominal fat distribution, and a positive family history of breast cancer have the greatest risk of developing breast cancer.

### Sex Hormones

Sex hormones, insulin levels, and nutritional factors are all involved in the etiology of breast cancer in obese women. Evidence that sex hormones are involved comes from studies of women who have had an oophorectomy at a young age. These women have a low incidence of breast cancer. Estrogen hormone replacement therapy is associated with a high risk of breast cancer, as is the use of oral contraceptives containing estrogen.<sup>9</sup>

In studies of premenopausal and postmenopausal obese women, with overall and central obesity, estradiol levels were higher than in lean women. Some of the obese women also had increased estrogen levels. Aromatase, the enzyme



**Fig 1. Rate ratios for the fitted incidence rate function according to quetelet index of relative body weight by menopausal status for a woman in a high- (H), moderate- (M), or low- (L) risk country. Rates are plotted relative to those for a woman with the same menstrual and reproductive characteristics whose quetelet index is 24 kg/m<sup>2</sup>. (Reprinted with permission.<sup>16</sup>)**

that converts androgens to estrogens, is present in fat tissue, and so with increased fat mass there is more conversion of androgens to estrogens. Obese patients also have less sex hormone-binding globulin (SHBG) than lean individuals. This adds to an increase in free estradiol levels, as well as other sex hormones, in obese people.<sup>19</sup>

The rate of estrogen metabolism to the less potent catechol estrogen is lower in obese than lean patients.<sup>9</sup> In addition, studies have shown that obese patients have increased free fatty acid levels. The excess free fatty acids compete with sex hormones for binding to SHBG, which results in higher levels of free estradiol.<sup>19</sup>

#### LUNG CANCER

Patients with a high BMI have an increased risk of colorectal cancer compared with individuals who have a low BMI.<sup>24</sup> However, the opposite is true for lung cancer.<sup>25</sup> Men and women with a BMI less than 28 have an increased risk of lung cancer compared with obese patients (Table 2). Smoking increases resting energy expenditure, which reduces the tendency to gain weight and become obese. Lean individuals may also have a lower intake of some nutrients, such as antioxidants, that could provide protection against lung cancer.

#### WEIGHT LOSS

A number of studies have assessed the effect of weight loss on the risk of cancer in obese patients and found no change in the risk of cancer with weight loss.<sup>26-27</sup> Another study found that the risk ratio for cancer mortality did not alter if patients lost weight, gained weight, or showed no change in body weight.<sup>28</sup> However, none of these studies has looked specifically at long-term weight loss.

**Table 2. Obesity and Lung Cancer: Adjusted Odds Ratio**

BMI	Current Smokers		Never Smokers	
	Men	Women	Men	Women
<22	2.0	2.0	0.9	2.9
25-27.9	1.2	1.2	0.8	1.9
>28	1.0	1.0	1.0	1.0

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#### LEAN POPULATIONS

In lean populations, including vegetarians, the standardized mortality ratios in men and women were lower for cancers of the intestinal system, stomach, and colon than for the general population.<sup>29</sup> The risk of these cancers was especially low for people who had been vegetarians for more than 20 years. Even in the vegetarian population, BMI influenced cancer risk; those with a low BMI had a lower risk of cancer than those with a high BMI.<sup>29</sup> However, vegetarians are characterized by many factors other than leanness that could explain their low risk of cancer.

#### CONCLUSION

In conclusion, there appears to be a relationship between cancer and obesity. There are many confounding factors that contribute to the development of cancer and which may explain the discordant findings. The relationship with obesity is particularly strong for endometrial, breast, and colon cancers, in which there is a positive relationship between weight gain and cancer risk, and for lung cancer, in which there is a negative relationship. Lean populations have a lower risk of cancer, but other factors such as altered eating habits may be important.

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