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The link between obesity and cancer

Otyłość a nowotwory

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S u m m a r y

Clinical and epidemiological prospective studies show a significant association between obesity and several cancers e.g. cancers of the colon, female breast (postmenopausal), endometrium, kidney (renal cell), and esophagus (adenocarcinoma). These data, and the year by year rising, worldwide trend in obesity, suggest that weight gain may be the largest avoidable cause of cancer in nonsmokers (1).

Although some of these associations can be explained by changes in the constitution of the human body or hormones associated with obesity, there are increases in a large variety of tumor types, suggesting that fundamental biological mechanisms may underlie these links.

The overwhelming majority of the data suggests that a combination of factors secreted by the adipocyte (increased leptin, decreased adiponectin and increased inflammatory cytokine secretion) with contributions from the secondary effects of obesity (such as hyperinsulinaemia and hyperlipidemia) lead to increased incidence of cancer (2).

Key words: obesity, cancer, metabolic syndrome

S t r e s z c z e n i e

Szereg badań klinicznych i epidemiologicznych pokazuje związek pomiędzy otyłością a nowotworami jelita grubego, rakiem piersi, endometrium, rakiem nerki czy przełyku. Dane te, jak i rosnące rozpowszechnienie otyłości sugerują, że przyrost wagi może być jednym z ważniejszych modyfikowalnych czynników wpływających na występowanie nowotworów (1).

Część powiązań pomiędzy otyłością i częstszym występowaniem niektórych typów nowotworów w tej grupie chorych może być wyjaśniona poprzez pewne zmiany funkcjonalne lub wpływ hormonów związanych z otyłością. Ważną rolę w procesie kancerogenezy odgrywają omówione w poniższym tekście mechanizmy biologiczne.

Zdecydowana większość danych sugeruje, że kombinacja czynników wydzielanych przez adipocyty (m.in. wzrost stężenia leptyny, obniżone stężenie adiponektyny i wzrost wydzielania cytokin zapalnych) oraz wpływ wtórnych do otyłości hiperinsulinemii i hiperlipidemii prowadzą do wzrostu zachorowań na raka (2).

Słowa kluczowe: otyłość, nowotwór, zespół metaboliczny

OBESITY AND CANCER

Human simple obesity is defined as an imbalance of elevated caloric intake and a relative lack of physical activity. Increased mass of the adipose tissue is associated with metabolic changes described as metabolic syndrome – characterized by abdominal obesity, reduced high-density lipoprotein (HDL) cholesterol levels, increased levels of triglycerides, hypertension and insulin resistance.

A relationship between excess body weight and mortality from all causes and from cardiovascular disease has been well-established in epidemiological studies (3-9).

The adverse metabolic effects of excess body fat are known to accelerate atherogenesis and increase the risk of coronary heart disease, stroke, and early death. Obesity could also influence the growth of cancers. The relationship between obesity and cancer risk has received less attention than its cardiovascular effects. Overweight women have increased risk of endometrial cancer and breast cancer after menopause (due to increased levels of circulating estrogen). Large prospective studies show a significant association between obesity and several cancers. Obesity can play a prominent role in the incidence and progression of cancers (1).

The International Agency for Research on Cancer (IARC) in 2002 concluded that there is sufficient evidence in humans for a cancer-preventive effect of weight gain avoidance (10). Accumulating data suggests that increased adiposity may increase incidence and/or death rates from a wide variety of human cancers, including colon and rectum, esophagus (*adenocarcinoma*), kidney (*renal cell carcinoma*), pancreas, gallbladder, ovary, cervix, female breast (postmenopausal), liver, prostate, and certain hematopoietic cancers (tab. 1). With regard to premenopausal breast cancer, the report concluded that available evidence on the weight gain avoidance has no benefit as a cancer-preventive factor. These data, and the rising worldwide trend in obesity, suggest that overeating may be the largest avoidable cause of cancer in nonsmokers. Few obese people are successful in long-term weight reduction, and thus there is little direct evidence regarding the impact of weight reduction on cancer risk.

For all other sites, IARC characterized the evidence for a cancer preventive effect of avoidance of weight gain as inadequate in humans for a cancer-preventive effect of intentional weight loss for any cancer site.

Table 1. The relative risk per 5 kg per m^2 increase in body mass index is reported for each site and sex.

Cancer type	Men (95% CI)	Women (95% CI)
Breast	ND	1.12 (1.08-1.16)
Colon	1.24 (1.20-1.28)	1.09 (1.05-1.13)
Endometrial	NA	1.59 (1.50-1.68)
Oesophageal	1.52 (1.33-1.74)	1.51 (1.31-1.74)
Kidney	1.24 (1.15-1.34)	1.34 (1.25-1.43)
Leukaemia	1.08 (1.02-1.14)	1.17 (1.04-1.32)
Melanoma	1.17 (1.05-1.30)	0.96 (0.92-1.01)
Myeloma	1.11 (1.05-1.18)	1.11 (1.07-1.15)
Non-Hodgkin's lymphoma	1.06 (1.03-1.09)	1.07 (1.00-1.14)
Pancreatic	1.07 (0.93-1.23)	1.12 (1.02-1.22)
Prostate	1.03 (1.00-1.07)	NA
Rectal	1.09 (1.06-1.12)	1.02 (1.00-1.05)
Thyroid	1.33 (1.04-1.70)	1.14 (1.06-1.23)

CI – confidence interval; NA – not applicable; ND – not determined. Relative risks are taken from a meta-analysis of data as reported in Renehan et al. (11) and Roberts et al. (12).

The evidence

There is sufficient evidence in experimental animals for a cancer-preventive effect of weight gain avoidance by diet restriction, based on studies of spontaneous or chemically induced cancers of the mammary gland, liver, pituitary gland (*adenoma*), pancreas, for chemically induced cancers of the colon, skin (*non melanoma*), and prostate, and for spontaneous and genetically induced *lymphoma*. An association between obesity and cancer at many sites is consistent with animal studies showing that diet restriction decreases spontaneous and carcinogen-induced tumor incidence, multiplicity and size (13-15).

Obesity does not appear to have the same effect on all types of cancers, nor to affect cancer risk in both sexes. One study found that obesity increases the risk of dying from all cancers by about 52% in men, but nearly doubles the risk of dying from any type of cancer in women (16). For some cancers, such as liver cancer, obesity was linked to about a five-fold increased risk of cancer mortality in men and women together.

The association between obesity and colon cancer mortality is not equally strong in both sexes, perhaps because body mass index (BMI) is a better measure of abdominal fat in men than women, or because of hormonal factors that are protective. Obesity-related breast cancer risk also varies by menopausal status. Increasing BMI levels are linked to a lower incidence of breast cancer in premenopausal women, but a greater incidence of breast cancer in postmenopausal women.

The influence of obesity on prostate cancer risk also varies. Although obesity is associated with a lower incidence of prostate cancer, studies suggest that obesity is linked to a greater risk of being diagnosed with a more aggressive form of prostate cancer, and studies have shown that obesity increases the risk of dying from prostate cancer. Growing evidence also indicates that obesity during childhood can increase the risk of childhood cancers, such as leukemia, and young-onset brain tumors.

HOW OBESITY CAN INCREASE CANCER RISK – THE MOLECULAR MECHANISMS

Obesity is strongly associated with changes in the physiological function of adipose tissue. These processes lead to insulin resistance, chronic inflammation, and altered secretion of adipokines. Adipose tissue plays an active role in endocrine signaling to the rest of the body. It has been shown in many studies that adipose tissue secretes molecules into the bloodstream, which signal to other metabolic organs or to the brain to coordinate responses to altered metabolic demands. These molecules – adipokines, can be secreted both from the adipocyte fraction and from the stromal-vascular fraction. Some of these adipokines have a great role in modulating the risk of cancer development. The most likely contributors from the adipose tissue itself are the adipokines – leptin, adiponectin and pro-inflammatory molecules (2).

Several of these factors, such as insulin resistance, increased levels of leptin, plasminogen activator inhibitor-1, and endogenous sex steroids, decreased levels of adiponectin, and chronic inflammation, are involved in carcinogenesis and cancer progression (17).

The variability in how obesity affects the incidence, progression, or mortality of various cancers suggests that these effects derive from multiple mechanisms, which animal research supports.

Fat tissue, by producing hormones and growth factors, and by fostering inflammation, could directly fuel the growth of tumors, thereby affecting cancer incidence, progression, recurrence, and survival rates.

All of these factors promote tumor initiation and growth. So, the possible mechanisms for cancerogenesis in obese include altered carcinogen metabolism, decreased oxidative DNA damage, greater DNA repair capacity (10), and a reduction of IGF-1 levels in diet restricted animals (13).

The imbalance in energy is caused by an excess of nutrients and it leads to oxidative stress and fatty acids metabolism abnormalities. It is conducive to inflammation and insulin resistance. This results in a number of processes that underlie cancer initiation and promotion, including DNA damage, cell division and migration, delayed cell death, an increase in blood vessel formation. The accelerated metabolism of fatty acids that occurs in obese individuals might increase DNA damage due to oxidation. In some evidence this DNA damage triggers a malignant transformation. The AKT-mTOR pathway is activated in obese animals, induces tumor cell growth and staves off tumor cell death. It has been implicated in a number of cancers and it is linked to an increased risk of developing a cancer, as well as to the progression of many cancers (fig. 1).

Cancer is a disorder with abnormal regulation of the growth and survival of cells. Fat cells generate many hormones, growth factors, and cytokines that can disrupt regulation of cell growth and survival. These molecular factors were estrogen, insulin, insulin like growth factor 1 (IGF-1), leptin, adiponectin, and adipokinase, as well as several mediators of inflammation (fig. 2).

Estrogen

The postmenopausal women are about 70% of all breast cancer patients. Most of the estrogen produced in postmenopausal women is derived from fat tissue via aromatase, the enzyme converting adrenal androgens into estrogen. The more fat tissue there is, the greater the levels of estrogen produced and in circulation. Such estrogen can fuel the growth of estrogen receptor – positive breast cancers. Studies show that mice made obese by being fed a high-fat diet and then inoculated with breast cancer cells had significantly greater tumor growth rates than mice similarly inoculated, but fed a normal diet (19). When inoculated obese mice were given an aromatase inhibitor, the tumor growth rate was markedly inhibited. Clinical studies confirm that circulating estradiol levels are linked to risk of recurrence of breast cancer. It does not explain the association of obesity with premenopausal breast cancer outcomes or with estrogen receptor – negative breast cancer outcomes (20). This mechanism also does not explain why estrogen is linked to both pre- and postmenopausal endometrial cancer risk (21).

Insulin

Another factor making obese women more susceptible to breast cancer recurrence and death is higher than normal insulin level, usually linked to obesity. BMI increase correlate closely with increases in fasting insulin levels in the nondiabetic population. Greater levels of insulin are linked to an increased risk of distant recurrence and death in breast cancer patients (22, 23).

The fetal version of the insulin receptor is overexpressed in breast cancer cells and can combine with itself or with IGF-1 to turn on the PI3K or Ras/Raf signaling pathways known to foster the growth of several types of cancers. In early-stage breast cancer women, total expression of the fetal insulin receptor is linked to worse survival rates, as is activation of the receptor by IGF-1. Insulin effects on breast cancer prognosis often are not apparent 5 years after diagnosis, suggesting that insulin may be an early mediator of the prognostic effects of obesity in breast cancer, other factors are going to be important later on. Leptin may be one of these factors. Higher levels of leptin are linked to an increased risk of distant recurrence and death from breast cancer – an effect that persists beyond 5 years postdiagnosis (24).

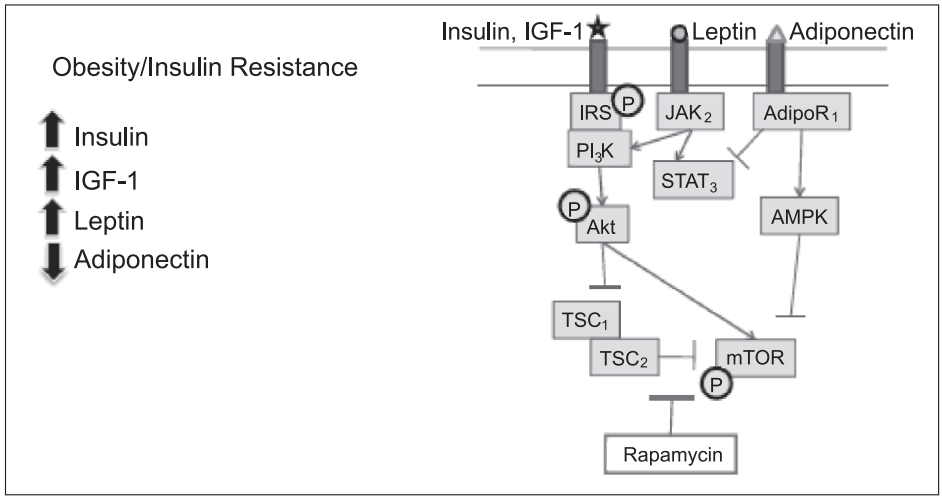

Fig. 1. Converging signaling pathways (18).
AdipoR – adiponectin receptor; AMPK – 5´adenosine monophosphateactivated protein kinase; IGF – insulin-like growth factor; IRS – insulin receptor substrate, JAK – Janus kinases; mTOR – mammalian target of rapamycin; P – phosphorylated; PI_3K – phosphoinositide 3-kinase; STAT – signal transducer and activator of transcription; TSC – tuberous sclerosis protein.

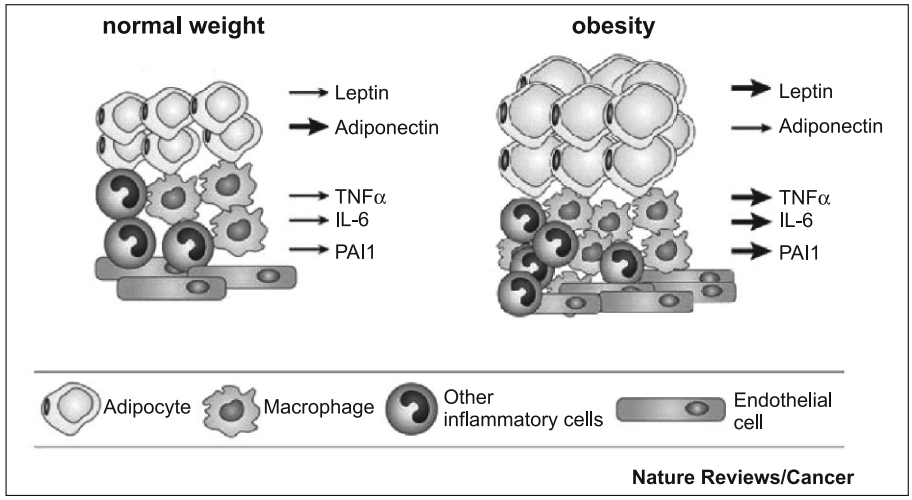

Fig. 2. Changes in adipose tissue in obesity (2).

OTHER MOLECULAR MECHANISMS

A number of other hormones, enzymes, and growth factors, that govern cellular energy balance and growth are thought to play a role in increasing cancer risk in obese individuals, including IGF, AMP kinase, leptin, adiponectin, inflammatory cytokines.

IGFs (insulin-like growth factors)

The IGFs stimulate cell growth and proliferation and inhibit apoptosis by activating the AKT signaling pathway. This pathway has been implicated in a number of cancers. IGFs are mitogens that regulate energy-dependent growth processes (25). The insulin-like growth factors (IGFs) may have roles, in addition to insulin, in cancer development. IGF-1 and IGF-2 are hormones produced primarily in the liver and they share sequence homology with insulin (26). Hyperinsulinaemia increases the production of IGF-1 in the liver (27). IGF-1 and IGF-2 are primarily expressed in the liver, but may also be expressed in neoplastic tissue. In fact, IGF-2 mRNA is the most highly upregulated transcript in colorectal cancer compared with normal colonic mucosa (28). Whether obesity is associated with increased IGF levels is controversial. Some studies have shown that obese patients with type 2 diabetes have higher circulating levels of IGF-1 and IGF-2 (29). However, obesity results in a reduction in growth hormone levels, which controls IGF-1 secretion, blunting effects on total IGF-1 levels (30). In this way obesity has a complex association with IGF1 serum levels.

AMP kinase

It is an enzyme that plays an important metabolic role, using its energy-sensing capabilities to trigger the cellular uptake of glucose and the breakdown of fatty acids when cells need more energy. AMP kinase also modulates insulin levels.

Leptin

An adipocyte-derived hormone known as leptin is the central mediator of a feedback loop that regulates appetite and energy homeostasis. Weight loss decreases leptin levels (31). A major physiological site of leptin action is in the central nervous system, but the leptin receptor (OBR; also known as LEPR) is also expressed at lower levels in peripheral tissues (32). Several studies have documented OBR expression in multiple cancers, including those of the breast, prostate and colon (33-35).

Adiponectin

This hormone regulates glucose uptake and the breakdown of fatty acids mainly by up-regulating AMP kinase. Adiponectin is linked to greater energy expenditure, and weight loss increases the amount of this hormone. Epidemiological studies have pointed to a link between adiponectin and carcinogenesis. Adiponectin levels were inversely associated with breast cancer risk in postmenopausal women in a prospective analysis (36). Adiponectin levels were also inversely correlated with the risk of endometrial and renal cell carcinoma (37, 38). However, in a later prospective study, adiponectin levels were not predictive of endometrial cancer risk (39).

The adiponectin-related mechanisms of cancerogenesis inhibition have been examined in several studies. Adiponectin inhibits prostate and colon cancer cell growth (40, 41).

The insufficiency of adiponectin is associated with mammary tumor development in mice, by down-regulating PTEN and up-regulating PI3K-AKT signaling (42).

Cell cycle progression is blocked in colon cancer by adiponectin, and its anti-proliferative effects were impaired by knockdown of the adiponectin receptors (41). Furthermore, adiponectin increased AMPK activity (AMP-activated kinase) – a key regulator of proliferation in response to nutrient status (43).

In response to adiponectin, HCC (*hepatocellular carcinoma cells*) had increased JNK phosphorylation, decreased mTOR phosphorylation and increased apoptosis (44). Cancers inoculated in adiponectin-deficient mice showed increased growth relative to controls, which was found to be due to reduced macrophage infiltration (45).

Animal models can help us understand how all these factors interact in the complex signaling that occurs in response to changes in caloric intake from the diet (46).

This research indicates that when mice are put on a calorie-restricted diet (30 percent less than normal), their IGF-1, insulin, and leptin levels decrease and adiponectin levels increase. In some, but not all, tissues, their AMP kinase levels also increase. Under these diet-restricted conditions, transplanted tumors do not grow, nor do tumors proliferate in response to the tumor promoter TPA. In contrast, mice with diet-induced obesity have elevated levels of IGF-1, insulin, and leptin and lower levels of adiponectin levels, and tumors grow rapidly. These results are seen for several different types of tumors.

To summarize, the association between cancer and obesity may be due to the convergence of pathways involving adipokines, inflammation and insulin resistance (fig. 3).

Inflammatory cytokines

The inflammatory cytokines were the first functional polypeptides secreted from fat tissue and to have a systemic role in metabolic homeostasis. Originally observed as an increase in tumor necrosis factor-α (TNFα) expression from fat in rodent obesity (47).

This response has also been shown to occur in humans and to involve the secretion of other cytokines, including interleukin-6 (IL-6) and plasminogen activator inhibitor 1 (PAI1; also known as SERPINE1) (48-50).

Insulin resistance associated with obesity is the effect of the cytokines secretion

TNFα has been implicated in the development of obesity-induced cancer in mice. The elimination of TNFα signaling by the deletion of the TNF receptor gene *Tnfrsf1a* (also known as *Tnfr1*) abrogates the ability of a high-fat diet to promote liver carcinogenesis that is induced by the chemical carcinogen diethyl-nitrosamine (DEN) (51).

The activation of the transcription factor – nuclear factor-κB (NF-κB) by inflammatory pathways is a potential mechanism of tumor promotion by obesity-linked inflammation.

NF-κB is activated by a variety of signals, including TNFα, Toll-like receptors and other inflammatory cytokines. The activation of NF-κB has been shown to be important in the development of cancers, including *glioblastoma*, *lymphoma* and pancreatic cancer. Activated NF-κB is required for cholestasis-induced liver cancer, which is a model of TNFα-induced cancer (52-55).

Another pro-inflammatory molecule, produced in adipose tissue, is the cytokine IL-6. Circulating IL-6 levels are correlated with BMI and adipose tissue is thought to account for up to 35% of circulating IL-6 in healthy subjects (56, 57).

IL-6 signals to the nucleus through signal transducer and activator of transcription 3 (STAT3) – an oncoprotein activated in a wide variety of cancers (58). In genetic and dietary models of obesity, the activation of STAT3 is increased in tumors growing in obese animals (51). STAT3 is activated by leptin, and may play a role in the pro-tumorigenic effects of this adipokine. Furthermore, the tumour-promoting effect of obesity on chemically induced hepatocellular carcinoma is eliminated in mice that lack endogenous IL-6 (51, 59).

OBESITY AND COLORECTAL CANCER

There are consistent data showing that obesity is associated with higher risk of colorectal cancer in men (relative risks of approximately 1.5-2.0) and women (relative risks of approximately 1.2-1.5) in both cases – control and cohort studies (10). Similar relationships are also seen for colon adenomas, with stronger associations for larger adenomas (60). There is also more recent evidence that obesity is linked to the risk of cancer progression. Large randomized colon cancer studies conducted by the National Surgical Adjuvant Breast and Bowel Project found that the people with Stage II or III colon cancer who fared the worst, in

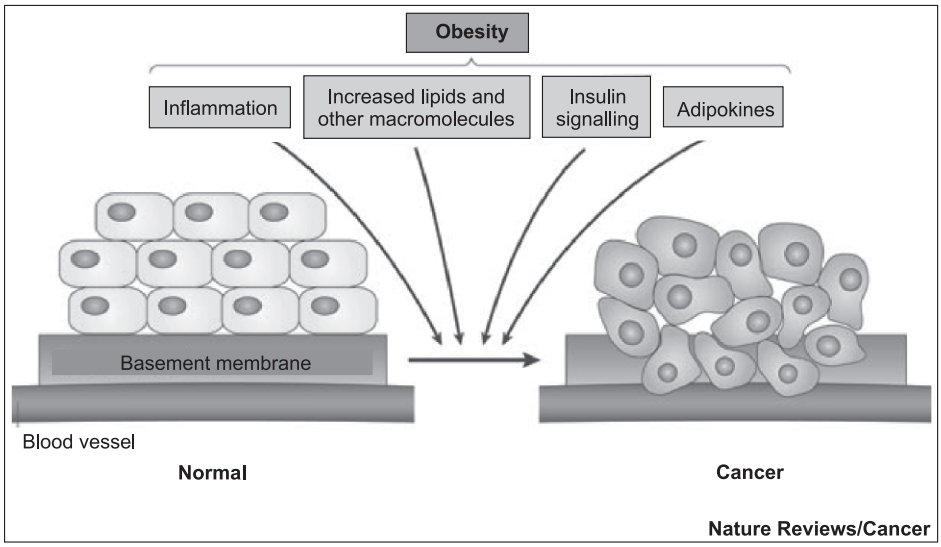

Fig. 3. Association between cancer and obesity – summary of pathways that may link obesity to cancer development (2).

terms of disease-free and overall survival, were those who were very obese (BMI greater than 36 kg/m^2) and the people who were underweight (but increased risk of mortality for underweight patients was dominated by non – colon cancer deaths) (61).

Stronger associations of colorectal cancer occurrence observed consistently across studies and populations have been seen in men than women. The reasons for the gender difference are speculative. One hypothesis is that central adiposity is a stronger predictor of colon cancer risk than peripheral adiposity or general overweight. As men are more likely to deposit fat centrally, BMI may be a more accurate indicator of the relevant exposure in men than in women. Support for the role of central obesity on colorectal cancer comes from studies suggesting that waist circumference and WHR are related strongly to risk of colorectal cancer and large adenomas in men (62). However, the association between WHR and colorectal cancer in women was not stronger than the association between BMI and colorectal cancer in several studies that examined both measures, making it unlikely that body fat distribution completely explains the gender differences. Another possible explanation is that there may be an offsetting beneficial effect of obesity on colorectal cancer risk in women. Substantial evidence supports the protective role of exogenous estrogens (in the form of postmenopausal hormone therapy) on the risk of colorectal cancer in women (63, 64). The high levels of circulating estrogens associated with postmenopausal obesity in women may diminish the obesity-associated risk of colorectal cancer. Giovannucci has proposed a mechanistic hypothesis that high body mass, and central obesity in particular, increased colon cancer risk through their effect on insulin production (62, 65, 66). Insulin and IGFs have been shown to promote the growth of colonic mucosal cells and colonic carcinoma cells *in vitro* studies (67, 68).

Higher risk of colorectal cancer has been associated with elevated fasting plasma glucose and insulin levels following a standard dose of oral glucose challenge and with elevated serum C-peptide levels (62, 69, 70). Several prospective cohort and case – control studies have found increased risk of colorectal cancer and large adenomas with increasing absolute levels of IGF-1 (70-74).

BREAST CANCER

Since the 1970s many epidemiological studies have assessed the association between anthropometric measures and breast cancer occurrence and/or prognosis (10). **The obesity – related risk of developing breast cancer varies by menopausal status.** It was established in early studies that the association between body size and risk of breast cancer differed according to menopausal status, and that heavier women were at increased risk of postmenopausal, but not premenopausal breast cancer (10). In fact, among premenopausal women, there is consistent evidence of a modest reduction in risk among women with high (> 28) BMI. This reduction in risk is likely due to the increased tendency for young obese women to have anovulatory menstrual cycles and lower levels of circulating steroid hormones (75).

Obesity has been shown consistently to increase rates of breast cancer in postmenopausal women by 30-50% (76-79). Some studies have found central adiposity to be an independent predictor of postmenopausal breast cancer risk beyond the risk attributed to overweight alone (1). Adult weight gain has generally been associated with a larger increase in risk of postmenopausal breast cancer than has BMI, in studies that examined both (1).

Studies of breast cancer mortality and survival among breast cancer cases illustrate that adiposity is associated both with poorer survival and increased likelihood of recurrence among those with the disease, regardless of menopausal status and after adjustment for stage and treatment (1). Very obese women (BMI 40.0) have breast cancer death rates that are three times higher than very lean (BMI < 20.5) women (1).

The data from Goodwin's research have shown that a BMI between 20 and 25 at breast cancer diagnosis is linked to the best outcome, with the lowest risk of distant recurrence or death (24). A recent metaanalysis of several studies of women diagnosed with breast cancer found that obesity is associated with a one-third increased risk for both breast cancer-specific mortality and all-cause mortality (83).

The higher risk of death among obese women likely reflects both a true biological effect of adiposity on survival and delayed diagnosis. Estrogen receptor (ER)-positive tumors are exposed to more continuous stimulation in obese than in normal BMI women. Studies have shown that the association between BMI and poorer prognosis is limited to or is more pronounced among women with ER-positive tumors and stage I and II disease (1). There is evidence that obese women are less likely to receive mammography screening and among women who self-detect their tumors, high BMI increases the likelihood of nonlocalized disease (1).

The association between BMI and postmenopausal breast cancer is stronger among women who have never used hormone replacement therapy (1).

It is likely that the high levels of circulating estrogens among women who use exogenous hormones, regardless of weight, obscure much or all of the association between BMI and breast cancer. The consistent observation that BMI is more strongly associated with breast cancer in women who do not use hormone replacement therapy supports the mechanistic hypothesis that BMI increases risk by increasing endogenous estrogen production. Furthermore, high levels of circulating estrogens and low levels of SHBG could be associated with increased risk of breast cancer in postmenopausal women (84).

The action of insulin and/or IGFs is probably another mechanism by which obesity may affect the risk

of breast cancer. IGF-1 is associated with mammary gland hyperplasia and mammary cancer (1).

It plays a role as a potent mitogen for normal and transformed breast epithelial cells in animals (1). Furthermore, receptors for IGF-1 are present in most human breast tumors and in normal breast tissue (1). In the two case-control studies and two prospective cohort studies positive associations between serum or plasma IGF-1 concentrations and breast cancer in premenopausal (but not postmenopausal) women have been shown (1). The magnitude of the association increased when both IGF-1 and IGF-binding protein 3 (IGFBP-3) were considered in two studies (1). The association with IGF-1 stronger in studies of premenopausal than postmenopausal breast cancer has been interpreted as suggesting that IGF-1 may increase risk only in the presence of high levels of endogenous estrogens (10).

Several studies show that elevated insulin levels or fasting glucose are linked to increased risk of distant recurrence and death in breast cancer patients and those levels tend to be higher in women with greater BMIs. Two case-control studies found that women with either premenopausal or postmenopausal breast cancer had increased circulating insulin or C-peptide levels. However, these findings were not confirmed in either pre- or postmenopausal women with breast cancer in a recent prospective cohort study (1).

ENDOMETRIAL CANCER

There are much convincing data from both case-control and cohort studies that overweight and obesity are strongly related to endometrial cancer (10). The risk of endometrial cancer increases linearly with increasing weight or BMI – it has been observed in most but not all studies (10, 16). The increase in risk generally ranges from two – to fourfold in overweight and/or obese women, and may be somewhat higher in studies of mortality than incidence (1). The causable mechanism for the increase in risk of associated with obesity endometrial cancer is the increase in circulating estrogens. The large increases in endometrial cancer risk among postmenopausal women who take unopposed estrogen (i.e. estrogen in the absence of progesterone) were observed in many studies, as well as increases in risk among women with higher circulating levels of total and bioavailable estrogens (1, 10).

KIDNEY CANCER

In overweight and obese compared to normal weight men and women the risk of renal cell cancer is 1.5- to 2.5-fold higher in worldwide study populations. Most studies have shown a dose-response relationship with increasing weight or BMI (10). Although at present this finding remains unexplained, in several studies, the increase in risk with increasing BMI is greater in women than in men (1, 16).

Interestingly, the risk of renal cell cancer associated with obesity was independent of blood pressure. It suggests that hypertension and obesity may influence renal cell cancer through different mechanisms (1).

The increased risk of kidney cancer seen in diabetics is probably caused by the hypothesis that chronic hyperinsulinemia contributes to the association of BMI and renal cell cancer (1).

ESOPHAGEAL CANCER

It has been established that obesity is associated with a two- to threefold increase in risk for *adenocarcinoma* of the esophagus (1,10). The associations was stronger in nonsmokers (1, 16). Higher BMI very often leads to gastroesophageal reflux and frequent reflux is very strongly associated with esophageal *adenocarcinoma* (1). Thus, the increased occurrence of reflux is hypothesized to explain the association of obesity and esophageal adenocarcinoma.

PROSTATE CANCER

There are some data from NIH-AARP Diet and Health Study which found that BMI was positively related with the risk of aggressive disease, while inversely associated with incidence of prostate cancer in general (Wright et al. 2007). The time of body fatness increase might be important in determining prostate cancer risk. Increased risk of aggressive, deadly prostate cancer may be linked to obesity that occurs before diagnosis when the tumor first develops or after diagnosis and removal of the prostate.

Weight gain before or around the time of diagnosis of prostate cancer can increase the risk of recurrence and death in men with prostate cancer (85). In one study obesity was found to be associated with adverse pathological features and a greater risk of biochemical progression (85-87).

Another study linked obesity pre-diagnosis to increased risk of death from prostate cancer (87). One study also found that men who became obese in the span from 5 years before to 1 year after prostatectomy have a greater risk of recurrence of their prostate cancer (88). Evidence is building that weight gain and obesity are risk factors for poor outcome in men diagnosed with prostate cancer, but there are many knowledge gaps that we need to fill and methodological issues that need to be addressed.

OTHER CANCERS

Few previous studies have shown the link between the risk of gall bladder cancer and obesity, but most have been relatively small. Available studies have consistently found elevated risks for women (of about twofold), but generally have had too few cases to evaluate the association in men (1, 16).

Obesity is the possible factor that can indirectly increase the risk of gallbladder cancer by increasing the risk of gallstones, which causes chronic inflammation leading to increased risk of biliary tract cancer (1).

However, smaller, earlier studies did not support an association but several recent studies have suggested that high BMI may be associated with approximately a doubling of risk for pancreatic cancer in men and women (1, 16). Further research is needed. Chronic hyperinsulinemia and glucose intolerance may lead to an increased risk of pancreatic cancer. This link has been suggested by the well-established positive association between diabetes and pancreatic cancer in prospective studies (1).

The link between ovarian cancer and obesity is not clear. Positive correlation between ovarian cancer and BMI has been in the range of 1.5-2.0 for the highest categories studied (1, 16). But several studies have not shown an association (1).

Smoking is the primary cause of lung cancer. But the lung cancer was also inversely associated with BMI. BMI has been reported to be inversely associated with lung cancer in several study populations that did not exclude smokers from the analysis (10). This finding is explained by the confounding effects of smoking (1). Studies that do not exclude smokers cannot separate the effects of BMI on the risk of death from the effects of smoking, namely, decreased BMI and increased risk of death. No association was seen between BMI and lung cancer in nonsmoking populations (16).

The data from the few studies have investigated the association of body mass with cancers of the liver, stomach, uterine cervix, and hematopoietic system. Three studies that have examined obesity and liver cancer found excess relative risk in both men and women in the range of 2.0-4.0 (1, 16). It has been found to be obesity related the risk for the gastric cardia adenocarcinoma (1), but data are limited and inconsistent for noncardia cancers of the stomach (1). Studies on BMI and cervical cancer are limited and inconclusive. In two prospective mortality studies positive associations with high BMI were found (two- to threefold increased risk) (1, 16). Interestingly, much smaller increased risks were observed in two cohorts of hospitalized patients diagnosed with obesity compared to rates in the general population (1).

When it comes to the relationship between hematopoietic cancers and BMI, the data are inconsistent (1, 16).

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