Obesity Biomarkers, Metabolism and Risk of Cancer: An Epidemiological Perspective

Katharina Nimptsch and Tobias Pischon

Abstract

Obesity is associated with metabolic alterations that may pose a biological link between body fatness and risk of cancer. Elucidating the role of obesity-related biomarkers in cancer development is essential for developing targeted strategies aiming at obesity-associated cancer prevention. Molecular epidemiological studies of the past decades have provided evidence that major hormonal pathways linking obesity and cancer risk include the insulin and insulin-like growth factor-1 (IGF-1) axis, sex-steroid hormones, adipokines and chronic low-grade inflammation. These pathways are interrelated with each other, and their importance varies by obesity-related cancer type. The insulin/IGF-1 axis has been implicated to play an important mediating role in the association between obesity and risk of pancreatic, colorectal and prostate cancer. Endogenous sex-steroid hormone concentrations, in particular obesity-associated pre-diagnostic elevations of estrogens and androgens, play an important role in postmenopausal breast cancer and endometrial cancer development. The adipokines adiponectin and leptin and adipocyte-mediated chronic low-grade inflammation represented by the acute-phase C-reactive protein may explain a substantial part of the association between obesity and risk of colorectal cancer. There is less evidence on whether these hormonal pathways play a mediating role in other obesity-associated types of cancer. In this chapter, the molecular epidemiologic evidence from prospective studies relating circulating obesity-related biomarkers to cancer risk is summarized, taking into account available evidence from Mendelian Randomization investigations aiming at improving causal inference.

K. Nimptsch (✉) · T. Pischon
Molecular Epidemiology Research Group, Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Robert-Rössle-Straße 10, 13125 Berlin, Germany
e-mail: katharina.nimptsch@mdc-berlin.de

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1 Introduction

Obesity is associated with metabolic alterations that may impact disease risk. The adipose tissue is not a mere energy storage but an active endocrine organ. Adipose tissue, in particular visceral fat, facilitates adverse metabolic effects such as insulin resistance and adipokine-mediated chronic low-grade inflammation that pose the link to chronic diseases [1, 2]. Major hormonal pathways that have been implicated to pose a biological link between body fatness and risk of obesity-associated types of cancer include the insulin and insulin-like growth factor axis, sex-steroid hormones, adipokines and chronic low-grade inflammation [3, 4]. It is unlikely that one of these suggested pathways accounts alone for the association between obesity and cancer. In contrast, these pathways are interrelated with each other in a complex manner and the importance of specific metabolic pathways varies by obesity-related cancer types (Fig. 1).

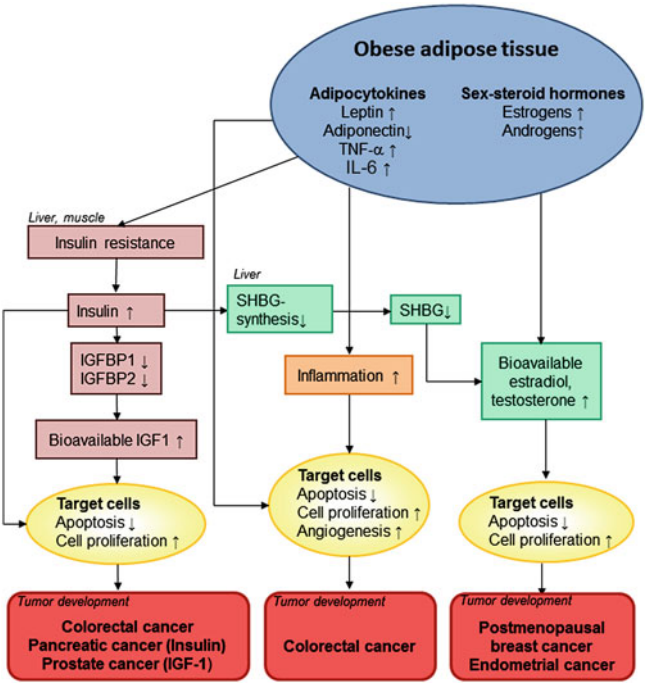

Fig. 1 Major hormonal pathways linking obesity with risk of cancer

During the past decades, a growing number of molecular epidemiological studies investigated the association between blood concentrations of obesity-related biomarkers and risk of cancer in order to examine whether the hypothesized pathways may explain the observed associations with obesity. The difficulty in conducting such studies is that the existence of a tumor may affect the biomarkers and metabolic pathways that are being investigated; therefore, traditional case–control studies that compare biomarker levels in diseased and non-diseased persons are of limited value in these instances. To avoid such possibility of reverse causation as much as possible, pre-diagnostic biomarker measurement is necessary, which requires a prospective cohort study design. In these studies, biomarker measurements are conducted among individuals free of cancer; study participants are then followed up over time for the incidence of cancer of interest; and biomarker levels at baseline are then related to cancer risk. It is evident that—depending on the incidence of the type of cancer of interest—such cohorts require large sample size. To be more cost efficient, often special study designs are applied, such as nested case–control or case–cohort designs embedded in large cohorts. In these studies, biomarker levels at baseline are measured among all incident cases but then compared to the levels of only a subgroup of the original cohort (case–cohort study) or to a number of matched controls that are selected using risk set sampling from the original cohort (nested case–control study). Such designs allow valid inferences about exposure–disease relationships that are almost identical to cohort analyses with only negligible loss of statistical efficiency. However, even in prospective study designs it cannot be excluded that occult cancer may have influenced findings or that other factors may explain the observed association between biomarkers and cancer risk. This possibility may be minimized by excluding cancer cases that were diagnosed shortly after blood collection from analysis and by careful adjustment for potential confounders. More recently, Mendelian Randomization studies have been found to be useful as a tool to investigate the association between biomarkers and cancer risk since these types of studies may circumvent reverse causation bias and confounding [5]. Thus, an advantage of the Mendelian Randomization approach is that genetic variants associated with lifelong differences in biomarker concentrations can be used as unbiased proxy variables, because on a population level, such variants are generally unrelated to lifestyle factors such as physical activity and diet that typically act as confounders in analyses relating obesity-related biomarkers to cancer risk. In this chapter, the molecular epidemiologic evidence from prospective studies relating circulating obesity-related biomarkers such as biomarkers of the insulin/IGF-1 axis, sex-steroid hormones, adipokines and inflammatory biomarkers to cancer risk is summarized. In addition, available evidence from Mendelian Randomization investigations aiming at improving causal inference in the association of obesity-related biomarkers with cancer risk is reviewed.

2 Insulin/IGF-Axis

There is abundant evidence that obesity is associated with insulin resistance and that weight loss improves insulin sensitivity [6]. The term insulin resistance refers to a condition in which skeletal muscles, liver and adipose tissue show a reduced response to insulin, i.e., a reduced insulin-mediated uptake of blood glucose as well as reduced fatty acid utilization by muscle cells and adipocytes, as well as reduced synthesis and storage of glycogen and decreased suppression of gluconeogenesis in the liver [7, 8]. Chronically elevated blood concentrations of insulin are typically a consequence of long-term insulin resistance, because more insulin is produced by the pancreatic beta cells in order to compensate for elevated blood glucose concentrations. This hyperinsulinemia, which also occurs in fasting states, has been hypothesized as one pathway explaining the positive association between obesity, especially abdominal obesity and elevated cancer risk. Chronically elevated insulin levels may affect cancer risk either through direct mitogenic effects or indirectly through the IGF-1 pathway [9]. Direct growth-promoting effects of insulin include suppression of apoptosis and promotion of cell proliferation [10]. The IGF-1 system is tightly linked to insulin metabolism. Both insulin and IGF-1 act as tissue growth factors and hormonal modulators of energy metabolism, with the difference that insulin mainly exerts short-term (post-prandial) effects whereas IGF-1 stimulates longer-term growth effects [9]. IGF-1 exerts mitogenic effects through anti-apoptotic properties [11]. The growth-promoting processes of insulin and IGF-1 are mediated by specific receptors (insulin receptor, IR; IGF-1 receptor, IGF1R) that are expressed on normal tissues but can also be expressed by neoplastic cells [9]. Interaction of insulin and IGF1R stimulate potentially carcinogenic pathways such as MAPK [12]. Hyperinsulinemia enhances the availability of free, bioactive IGF-1 by upregulating hepatic IGF-1 synthesis on the one hand and downregulating the hepatic production of two binding proteins (IGFBP-1 and IGFBP-2) on the other hand. However, evidence linking obesity to circulating IGF-1 concentrations is mixed and the relationship seems to be nonlinear with highest concentrations of IGF-1 observed in moderately overweight individuals [13, 14].

The relatively frequently observed concurrent occurrence of type 2 diabetes and cancer gave a first plausible hint that hyperinsulinemia, which is commonly observed in diabetics, may play a role in carcinogenesis. Comparing diabetics with non-diabetics, a higher risk of cancer of the pancreas, liver, breast, colorectum, urinary tract and female reproductive organs was observed, with strongest associations (about twofold higher risk) for cancers of the liver, pancreas and endometrium [15].

Serologic evidence for a role of hyperinsulinemia in carcinogenesis comes from prospective studies in which pre-diagnostic biomarkers of insulin metabolism were related to later cancer risk. Because insulin is produced by pancreatic beta cells, the pancreas is immediately exposed to chronically high insulin synthesis. In addition, high expression of IGF-1 as well as of both insulin and IGF-1 receptors has been observed in pancreatic cancer cell lines [16, 17]. Pre-diagnostic insulin

concentrations were associated with higher risk of pancreatic cancer in a large prospective cohort of male smokers [18] as well as in an analysis pooling data from five prospective US cohort studies [19]. In both these analyses, associations with insulin became stronger after exclusion of patients diagnosed with pancreatic cancer within 10 years of their blood collection, suggesting that observed associations are not due to reverse causation bias. In contrast, evidence for an association between pre-diagnostic concentrations of IGF-1 or the ratio of IGF-1 to IGFBP-3, a marker of free IGF-1, and risk of pancreatic cancer is weak. While weak positive associations with free IGF-1 have been observed in a large US cohort [20] and a prospective study from Japan [21], no associations were observed in the European Prospective Investigation into Cancer and Nutrition (EPIC) [22] and a pooled analysis of four US cohorts [23].

The insulin and IGF-1 pathway may also explain at least part of the association between obesity and higher risk of colorectal cancer. In the EPIC study, circulating C-peptide at baseline as indicator for long-term insulin secretion was associated with higher risk of colorectal cancer [24]. Also a meta-analysis of prospective cohort studies suggests a positive association of biomarkers of insulin metabolism (C-peptide or fasting insulin) and colorectal cancer risk [25]. In terms of circulating IGF-1, no association was observed in EPIC, but a meta-analysis including the findings in EPIC and ten other prospective cohorts found that high pre-diagnostic IGF-1 concentrations were associated with a moderately higher risk of colorectal cancer [26].

Studies investigating biomarkers of insulin metabolism in relation to risk of postmenopausal breast cancer have not observed consistent positive associations [25, 27–30], but there is evidence that IGF-1 is modestly associated with higher risk of breast cancer independent of menopausal status from a pooled analysis of data from 17 prospective studies [13]. With respect to endometrial cancer, as to date a limited number of prospective studies have investigated pre-diagnostic biomarkers of the insulin/IGF-1 pathway in relation to disease risk. In a nested case–control study of the Women's Health Initiative (WHI), however, a strong positive association between fasting insulin and risk of endometrial adenocarcinoma (making up 82 % of all endometrial cancer cases) was observed among women not using hormone therapy, and the association was slightly attenuated after adjustment for BMI [31]. Counterintuitively, however, in the same study pre-diagnostic IGF-1 concentrations were inversely associated with risk of endometrial cancer. A meta-analysis including four prospective studies on IGF-1 and risk of ovarian cancer did not provide evidence for this pathway [32]. While epidemiologic evidence relating circulating insulin or C-peptide [33–39] to risk of prostate cancer is inconclusive, pre-diagnostic circulating IGF-1 concentrations have been consistently related to higher risk of prostate cancer, especially low-grade tumors [40]. Prospective investigations on insulin/IGF-1 and risk of liver cancer are scarce, although higher pre-diagnostic concentrations of C-peptide have been related to higher risk of liver cancer in EPIC [41]. Prospective studies on the association of circulating insulin, C-peptide or IGF-1 and other obesity-associated cancers such as renal cell cancer and esophageal adenocarcinoma are as to date scarce.

In summary, hyperinsulinemia may potentially explain at least part of the positive association between obesity and risk of pancreatic cancer and colorectal cancer, whereas a role of IGF-1 is implicated for colorectal cancer and prostate cancer. Evidence is less clear for other obesity-associated types of cancer. Future research should consider Mendelian Randomization studies investigating genetically determined higher insulin or IGF-1 in relation to risk of colorectal or pancreatic cancer, which could improve causal inference by circumventing reverse causation and residual confounding. We are aware of only one previous Mendelian Randomization study in this context, which observed that genetically determined higher insulin was associated with higher risk of endometrial cancer, supporting a causal association of insulin in endometrial cancer etiology [42].

3 Sex-Steroid Hormones

Adiposity is associated with higher formation of endogenous sex-steroid hormones including estrogens, progesterone and androgens, especially in postmenopausal women [43]. In addition, obesity-related hyperinsulinemia and the consequential high bioactivity of IGF-1 reduce the hepatic secretion of sex hormone-binding globulin (SHBG), which results in higher bioavailability of sex-steroid hormones. Alterations in sex-steroid hormones have been suggested to explain a large proportion of the association of obesity with postmenopausal breast cancer and endometrial cancer [3]. Thus, clinical and experimental evidence suggests that sex-steroid hormones, in particular estrogen and progesterone, play an important role in the regulation of cell proliferation and apoptosis in breast cancer and endometrial cancer [3]. Many established risk factors of both breast and endometrial cancers such as early menarche, late menopause, estrogen replacement therapy but also obesity are related to the lifetime exposure to estrogen. Epidemiologic investigations have provided evidence that endogenous sex-steroid hormone concentrations are related to later risk of both postmenopausal breast cancer and endometrial cancer. In the EPIC study, it was shown that total and bioavailable androgens and estrogens were associated with approximately twofold higher risk of postmenopausal breast cancer [44]. The study also showed that both BMI and waist circumference were positively associated with free testosterone, estrone and estradiol and the positive association between BMI and risk of postmenopausal breast cancer was attenuated substantially after adjustment for total or free estrogens. Similarly, in a pooled analysis of nine earlier prospective studies, sex-steroid hormones including testosterone, estrone and estradiol were associated with higher postmenopausal breast cancer risk and the positive association with BMI was largely accounted for by adjustment for estradiol [45]. These observations provide convincing evidence that a substantial proportion of the association between obesity and risk of postmenopausal breast cancer can be explained by the obesity-related alterations in sex-steroid hormone concentrations.

With respect to endometrial cancer, there is evidence that high estradiol may not only lead to higher cell proliferation and less apoptosis, but also exert cancer-promoting effects through upregulation of IGF-1 synthesis in endometrial tissue [46]. The relationship between sex-steroids hormones and endometrial cancer has been described within the framework of the "unopposed estrogen hypothesis", which implicates that women with high endogenous concentrations of the mitogenic estrogen may be at increased endometrial cancer risk especially when these are not or insufficiently counterbalanced by progesterone, which stimulates the metabolism of estradiol and inhibits IGF-1 actions [3, 47]. Epidemiological studies have observed higher endometrial cancer risk associated with high blood concentrations of estrogens in postmenopausal women. Furthermore, higher levels of endogenous androgens, i.e., androstenedione and testosterone, have been related to higher endometrial cancer risk in pre- and postmenopausal women [47]. In line with these observations, women with polycystic ovary syndrome, a condition related to higher androgen concentrations and hyperinsulinemia, are at increased risk of endometrial cancer [48]. In a nested case–control study combining data from three prospective cohort studies, a strong association of pre-diagnostic blood concentrations of estrogens and androgens with endometrial cancer risk was observed in postmenopausal women [43].

Although androgens play an important role in the physiological growth of the prostate and despite the fact that androgen deprivation therapy is a standard therapy for prostate cancer, pre-diagnostic blood concentrations of sex-steroid hormones (androgens and estrogens) are unlikely to play a role in the development of prostate cancer as results from a pooled analysis of 18 prospective studies have shown [49]. Similarly, the limited number of studies relating pre-diagnostic sex-steroid hormones to ovarian cancer risk is not supportive of blood estrogen levels playing an important role and provides limited evidence for a role of circulating androgens in this gynecological obesity-associated type of cancer [50, 51].

In summary, while there is good evidence for sex-steroid hormones explaining a large proportion of the positive association between obesity and risk of postmenopausal breast cancer and endometrial cancer, this pathway is less likely to be of importance in other obesity-associated types of cancer.

4 Adipokines

Soluble substances produced by adipose tissue have been collectively named adipocytokines or adipokines [8]. These adipocyte-derived hormones have been suggested to play a role in the pathogenesis of obesity-associated cancers. Adiponectin and leptin are the most abundantly produced adipokines compared with other adipokines such as resistin, plasminogen activator inhibitor (PAI)-1 or hepatocyte growth factor (HGF). Other substances produced by adipose tissue include a number of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and others.

4.1 Adiponectin

In contrast to many other adipokines, adiponectin expression is downregulated in obese adipose tissue. Thus, lower adiponectin concentrations are observed in obese individuals compared with normal-weight individuals [52]. Adiponectin plays an important role in energy metabolism and has insulin-sensitizing and anti-inflammatory properties [8, 53]. In addition, anti-neoplastic properties such as inhibition of proliferation and promotion of apoptosis have been observed to be upregulated by adiponectin in cancer cells [54]. High adiponectin concentrations have been suggested to play a protective role in the development of cancer either directly through inhibition of cell growth and induction of apoptosis or indirectly through improved insulin sensitivity and reduced inflammation [54]. Epidemiological evidence for an association between pre-diagnostic adiponectin concentrations and obesity-associated cancer has emerged from several investigations. In EPIC, higher circulating adiponectin concentrations were associated with a lower risk of colorectal cancer [55]. Furthermore, non-high-molecular-weight (HMW) adiponectin, which has a higher anti-inflammatory potential than HMW-adiponectin, was particularly associated with lower risk of colorectal cancer. In nested case–control studies of two large US-based prospective cohort studies, pre-diagnostic adiponectin concentrations were associated with lower risk of colorectal cancer only in men but not in women [56]. Similar sex differences were observed in a meta-analysis that included 13 epidemiological studies—both case–control and prospective studies—in which a weak inverse association between adiponectin and colorectal neoplasia was observed in men but not in women [57]. However, in this meta-analysis, stronger associations were observed in smaller studies and studies of lower quality, suggesting that the true association between adiponectin and colorectal cancer might have been overestimated. Studies on the association between genetic variants in the *ADIPOQ* gene and risk of colorectal cancer have produced diverse findings. In a meta-analysis including six case–control studies, three polymorphisms in the *ADIPOQ* gene were associated with colorectal cancer, but associations were restricted to Asian populations while not seen in Caucasian populations [58]. In a pooled analysis of epidemiological studies on colorectal cancer where genetic markers were also available, polymorphisms in the *ADIPOQ* gene that have been identified in genome-wide association studies on adiponectin concentrations were not related to colorectal cancer risk [59], arguing against a causal contribution of adiponectin in the association between obesity and colorectal cancer. Whether adiponectin may play a mediating role in the association of obesity and other types of cancers has been less often investigated. In a case–cohort investigation of the WHI, higher adiponectin concentrations tended to be associated with lower risk of postmenopausal breast cancer [60]. This inverse association did not persist after adjustment for insulin, suggesting that part of the association observed with adiponectin is explained by insulin, which is also mechanistically plausible. In a nested case–control study of male smokers, an inverse association between pre-diagnostic adiponectin and risk of renal cell carcinoma was observed, which accounted for a large proportion in the positive

association between BMI and renal cell carcinoma [61]. On the other hand, no association between circulating adiponectin and risk of endometrial cancer, the cancer type that shows the strongest association with obesity, was observed in the Nurses Health Study, but the number of included cases was limited [62]. Interestingly, adiponectin, in particular HMW-adiponectin, has been associated with higher risk of hepatocellular carcinoma in two nested case–control studies of prospective cohorts including EPIC [63, 64], but not in another nested case–control study [65]. Overall, these mixed observations support the need of future prospective studies to clarify the potentially mediating role of adiponectin in obesity-associated cancer.

4.2 Leptin

Leptin is a classical adipokine that is primarily expressed by adipose tissue [66]. Thus, circulating leptin reflects adipose tissue mass and, typically, leptin is found in higher concentrations in obese compared with lean individuals [67]. The physiological function of leptin is long-term modulation and regulation of dietary intake and energy balance [68]. Besides, there is mechanistic evidence that leptin may explain the positive association between obesity and risk of cancer. Experimental studies have demonstrated cancer-promoting activities of leptin, such as promotion of cell proliferation, migration and angiogenesis and inhibition of apoptosis [69]. In addition, it has been demonstrated that leptin receptor is expressed in human colon and breast cancer cell lines, which points to a role of leptin in the growth of these cancers [69, 70]. There is some evidence from epidemiological studies investigating circulating leptin concentrations and risk of obesity-related cancer, but most evidence exists for colorectal cancer [69]. In a prospective study from Sweden, higher circulating leptin was associated with higher risk of colon cancer in men but not in women [71]. Similarly, in EPIC pre-diagnostic leptin was associated with higher colon cancer risk only in men, while in women no association was observed [72]. A positive association between pre-diagnostic circulating leptin concentrations and risk of colon cancer in men was also observed in a study from Norway [73]. A higher risk of colorectal cancer in women with high pre-diagnostic leptin concentrations was observed in the Japan Collaborative Cohort Study [74] and in the WHI cohort [75]. In a meta-analysis including six prospective studies, higher leptin concentrations were significantly associated with higher risk of colorectal cancer [76]. Interestingly, soluble leptin receptor (sOB-R), which determines the bioactivity of leptin, was strongly inversely associated with risk of colorectal cancer in EPIC [72]. In two US cohorts, soluble leptin receptor was not associated with higher overall colorectal cancer risk in either men or women, although high sOB-R concentrations were associated with higher rectal cancer risk in women [56]. A positive association between genetic variation in *LEP* and colorectal cancer risk has been observed [77], but so far no Mendelian Randomization study has been conducted to improve causal inference.

Less epidemiological studies have been conducted to elucidate whether leptin may play a mediating role in the association between obesity and other types of cancer, and the few studies on breast cancer, endometrial cancer and pancreatic cancer were not conclusive so far [69].

4.3 Other Adipokines

There is limited evidence on the association between pre-diagnostic concentrations of other adipokines such as resistin and cancer incidence. Resistin is a relatively newly discovered adipokine that may mediate the association between obesity and cancer through insulin and inflammatory pathways [76]. In the WHI, resistin was associated with nonsignificantly higher risk of colorectal cancer but the positive association was mainly accounted for by insulin concentrations [75]. With respect to postmenopausal breast cancer, no associations with resistin were observed [60]. In a cohort of male smokers, no association between resistin and risk of renal cell carcinoma was reported [61]. The investigation of the role of novel adipokines deserves further attention in future research in obesity and cancer.

5 Inflammatory Markers

There is convincing evidence that obesity is associated with chronic low-grade inflammation triggered by adipocyte-derived production of pro-inflammatory cytokines (e.g., tumor necrosis factor alpha, interleukin-6) which stimulate the hepatic secretion of acute-phase proteins, such as C-reactive protein (CRP) [4]. In 1863 Rudolf Virchow postulated inflammation as the origin of cancer based on his clinical observations that cancer often arises from sites of local chronic inflammation, which is observed also nowadays [78]. There is plausible evidence that chronic inflammation plays an etiologic role in colorectal carcinogenesis, as it has been consistently observed that individuals with chronic inflammatory bowel diseases have a higher risk of colorectal cancer [79, 80]. In addition, the use of aspirin and other anti-inflammatory drugs has been associated with a lower risk of colorectal cancer, which gives further support for a role of inflammation in colorectal carcinogenesis [81–84]. Obesity-associated chronic low-grade inflammation [4] may play an important role in colorectal carcinogenesis through fostering cell proliferation, cell survival and migration [85]. Therefore, at least part of the positive association between obesity and colorectal cancer may be explained by inflammatory processes. In support of this hypothesis, it was shown that diet-induced weight loss reduced chronic inflammation in the colorectal mucosa of obese individuals accompanied by downregulation of inflammatory and cancer gene pathways [86]. A number of epidemiological studies investigated the association between biomarkers of chronic inflammation, particularly CRP and colorectal cancer risk. High blood concentrations of CRP have been associated with moderately higher

CRC risk in several prospective studies [87–89] including in the EPIC study [90]. However, findings from observational studies relating circulating CRP to cancer risk may not necessarily reflect causal associations. Despite a prospective study design, it is possible that pre-clinical disease leads to inflammatory processes before symptomatic disease diagnosis, which may result in false-positive associations due to reverse causation. Furthermore, residual confounding cannot be excluded. In a Mendelian Randomization analysis within EPIC, genetically determined higher CRP concentrations due to four SNPs in the *CRP* gene were associated with higher risk of colorectal cancer, which is in line with the hypothesis that CRP plays a causal role in colorectal carcinogenesis [91]. Interestingly, very similar results were obtained in a Mendelian Randomization study employing 20 CRP-related SNPs within a US cohort with colorectal cancer, whereas no association was observed for breast cancer [92]. Genetically determined higher CRP concentrations were not associated with higher risk of overall cancer in another Mendelian Randomization analysis [93]. However, all these studies had limited sample size for deriving robust evidence from Mendelian Randomization. Therefore, larger Mendelian Randomization studies on inflammatory markers and cancer risk are warranted. Other inflammatory cytokines such IL-6 have been less often investigated, but a meta-analysis of six prospective studies of circulating IL-6 found a borderline statistically significant positive association with colorectal cancer risk [94].

There is less evidence for inflammatory markers playing a role in other types of obesity-related cancer. However, in the EPIC study, pre-diagnostic concentrations of both IL-6 and CRP were positively associated with hepatocellular carcinoma [63]. Furthermore, in the WHI, CRP was associated with higher risk of postmenopausal breast cancer and the association between BMI and postmenopausal breast cancer was substantially attenuated after adjusting for CRP, which indicates a mediating role in the obesity–breast cancer association [60].

6 Mediating Effect of Biomarkers in the Obesity–Cancer Association

Although there is a variety of studies investigating specific obesity-related biomarkers and their association with cancer incidence, only few investigations took various biomarkers in the obesity pathway simultaneously into account and formally examined their mediating role in the obesity–cancer association.

In a case–cohort analysis within the WHI, the mediating effects of estradiol, insulin and CRP in the association between obesity and risk of postmenopausal breast cancer were evaluated [60]. The results showed that the association between BMI and breast cancer risk was completely attenuated after adjustment for circulating estradiol, insulin and CRP, with insulin and CRP being the most important mediators. In another case–cohort investigation of the WHI, the positive association between waist circumference and risk of colorectal cancer was by 50 % attenuated after adjustment for leptin and insulin concentrations [75]. These first investigations

taking the large spectrum of biomarkers simultaneously into account give important insights into which factors are the most promising targets for prevention of obesity-associated cancer morbidity. More such comprehensive analyses are warranted.

7 Conclusions

The molecular epidemiologic research of the past decades has provided important insights into potential metabolic mechanisms linking obesity with higher risk of cancer. However, as to date, the underlying mechanisms of the obesity–cancer association are not fully understood. The metabolic pathways insulin/IGF-1, sex-steroid hormones, adipokines and inflammation are likely to explain part of the positive association between obesity and higher risk of certain types of cancer. The insulin/IGF-1 axis has been implicated to play an important role in the association between obesity and risk of pancreatic, colorectal and prostate cancer. Obesity-associated pre-diagnostic elevations of endogenous sex-steroid hormone concentrations, in particular estrogen and progesterone, play an important role in postmenopausal breast cancer and endometrial cancer. The adipokines adiponectin and leptin and adipocyte-mediated chronic low-grade inflammation represented by the acute-phase CRP may explain a substantial part of the association between obesity and risk of colorectal cancer. Whether these obesity-related biomarkers really play a causal role in carcinogenesis deserves further investigation, ideally through adequately powered Mendelian Randomization studies utilizing knowledge on genetic determinants of obesity-related biomarkers derived from genome-wide association studies. In addition, more studies investigating various implicated obesity-associated biomarkers simultaneously in order to quantify their individual mediating role will pave the way for targeted pharmacological or lifestyle interventions aiming at obesity-associated cancer prevention through modification of the most important biomarkers.

References

1. Britton KA, Massaro JM, Murabito JM, Kreger BE, Hoffmann U, Fox CS (2013) Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. J Am Coll Cardiol 62(10):921–925. doi:10.1016/j.jacc.2013.06.027
2. Despres JP (2012) Body fat distribution and risk of cardiovascular disease: an update. Circulation 126(10):1301–1313. doi:10.1161/CIRCULATIONAHA.111.067264
3. Calle EE, Kaaks R (2004) Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev 4(8):579–591. doi:10.1038/nrc1408
4. Roberts DL, Dive C, Renehan AG (2010) Biological mechanisms linking obesity and cancer risk: new perspectives. Annu Rev Med 61:301–316. doi:10.1146/annurev.med.080708.082713

5. Davey Smith G, Ebrahim S (2003) 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol 32(1):1–22
6. Reaven GM (2011) Insulin resistance: the link between obesity and cardiovascular disease. Med Clin N Am 95(5):875–892. doi:10.1016/j.mcna.2011.06.002
7. Kaaks R, Lukanova A (2001) Energy balance and cancer: the role of insulin and insulin-like growth factor-I. Proc Nutr Soc 60(1):91–106
8. Tilg H, Moschen AR (2006) Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 6(10):772–783. doi:10.1038/nri1937
9. Pollak M (2008) Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev 8 (12):915–928
10. Giovannucci E (2001) Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 131(11 Suppl):3109S–3120S
11. Renehan AG, Frystyk J, Flyvbjerg A (2006) Obesity and cancer risk: the role of the insulin-IGF axis. Trends Endocrinol Metab (TEM) 17(8):328–336. doi:10.1016/j.tem.2006.08.006
12. Giovannucci E (2003) Nutrition, insulin, insulin-like growth factors and cancer. Horm Metab Res = Hormon- und Stoffwechselforschung = Hormones et metabolisme 35(11–12):694–704. doi:10.1055/s-2004-814147
13. Key TJ, Appleby PN, Reeves GK, Roddam AW (2010) Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. Lancet Oncol 11(6):530–542. doi:10.1016/S1470-2045(10)70095-4
14. Fowke JH, Matthews CE, Yu H, Cai Q, Cohen S, Buchowski MS, Zheng W, Blot WJ (2010) Racial differences in the association between body mass index and serum IGF1, IGF2, and IGFBP3. Endocr Relat Cancer 17(1):51–60. doi:10.1677/ERC-09-0023
15. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R (2009) Diabetes and cancer. Endocr Relat Cancer 16(4):1103–1123. doi:10.1677/ERC-09-0087
16. Ohmura E, Okada M, Onoda N, Kamiya Y, Murakami H, Tsushima T, Shizume K (1990) Insulin-like growth factor I and transforming growth factor alpha as autocrine growth factors in human pancreatic cancer cell growth. Cancer Res 50(1):103–107
17. Trajkovic-Arsic M, Kalideris E, Siveke JT (2013) The role of insulin and IGF system in pancreatic cancer. J Mol Endocrinol 50(3):R67–R74. doi:10.1530/JME-12-0259
18. Stolzenberg-Solomon RZ, Graubard BI, Chari S, Limburg P, Taylor PR, Virtamo J, Albanes D (2005) Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. JAMA 294(22):2872–2878. doi:10.1001/jama.294.22.2872
19. Wolpin BM, Bao Y, Qian ZR, Wu C, Kraft P, Ogino S, Stampfer MJ, Sato K, Ma J, Buring JE, Sesso HD, Lee IM, Gaziano JM, McTiernan A, Phillips LS, Cochrane BB, Pollak MN, Manson JE, Giovannucci EL, Fuchs CS (2013) Hyperglycemia, insulin resistance, impaired pancreatic beta-cell function, and risk of pancreatic cancer. J Natl Cancer Inst 105(14):1027–1035. doi:10.1093/jnci/djt123
20. Douglas JB, Silverman DT, Pollak MN, Tao Y, Soliman AS, Stolzenberg-Solomon RZ (2010) Serum IGF-I, IGF-II, IGFBP-3, and IGF-I/IGFBP-3 molar ratio and risk of pancreatic cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomark Prev 19(9):2298–2306. doi:10.1158/1055-9965.EPI-10-0400
21. Lin Y, Tamakoshi A, Kikuchi S, Yagyu K, Obata Y, Ishibashi T, Kawamura T, Inaba Y, Kurosawa M, Motohashi Y, Ohno Y (2004) Serum insulin-like growth factor-I, insulin-like growth factor binding protein-3, and the risk of pancreatic cancer death. Int J Cancer 110 (4):584–588. doi:10.1002/ijc.20147
22. Rohrmann S, Grote VA, Becker S, Rinaldi S, Tjonneland A, Roswall N, Gronbaek H, Overvad K, Boutron-Ruault MC, Clavel-Chapelon F, Racine A, Teucher B, Boeing H, Drogan D, Dilis V, Lagiou P, Trichopoulou A, Palli D, Tagliabue G, Tumino R, Vineis P, Mattiello A, Rodriguez L, Duell EJ, Molina-Montes E, Dorronsoro M, Huerta JM, Ardanaz E, Jeurnink S, Peeters PH, Lindkvist B, Johansen D, Sund M, Ye W, Khaw KT, Wareham NJ,

Allen NE, Crowe FL, Fedirko V, Jenab M, Michaud DS, Norat T, Riboli E, Bueno-de-Mesquita HB, Kaaks R (2012) Concentrations of IGF-I and IGFBP-3 and pancreatic cancer risk in the European prospective investigation into cancer and nutrition. Br J Cancer 106(5):1004–1010. doi:10.1038/bjc.2012.19

23. Wolpin BM, Michaud DS, Giovannucci EL, Schernhammer ES, Stampfer MJ, Manson JE, Cochrane BB, Rohan TE, Ma J, Pollak MN, Fuchs CS (2007) Circulating insulin-like growth factor axis and the risk of pancreatic cancer in four prospective cohorts. Br J Cancer 97(1):98–104. doi:10.1038/sj.bjc.6603826
24. Jenab M, Riboli E, Cleveland RJ, Norat T, Rinaldi S, Nieters A, Biessy C, Tjonneland A, Olsen A, Overvad K, Gronbaek H, Clavel-Chapelon F, Boutron-Ruault MC, Linseisen J, Boeing H, Pischon T, Trichopoulos D, Oikonomou E, Trichopoulou A, Panico S, Vineis P, Berrino F, Tumino R, Masala G, Peters PH, van Gils CH, Bueno-de-Mesquita HB, Ocke MC, Lund E, Mendez MA, Tormo MJ, Barricarte A, Martinez-Garcia C, Dorronsoro M, Quiros JR, Hallmans G, Palmqvist R, Berglund G, Manjer J, Key T, Allen NE, Bingham S, Khaw KT, Cust A, Kaaks R (2007) Serum C-peptide, IGFBP-1 and IGFBP-2 and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition. Int J Cancer 121(2):368–376. doi:10.1002/ijc.22697
25. Pisani P (2008) Hyper-insulinaemia and cancer, meta-analyses of epidemiological studies. Arch Physiol Biochem 114(1):63–70
26. Rinaldi S, Cleveland R, Norat T, Biessy C, Rohrmann S, Linseisen J, Boeing H, Pischon T, Panico S, Agnoli C, Palli D, Tumino R, Vineis P, Peeters PH, van Gils CH, Bueno-de-Mesquita BH, Vrieling A, Allen NE, Roddam A, Bingham S, Khaw KT, Manjer J, Borgquist S, Dumeaux V, Torhild Gram I, Lund E, Trichopoulou A, Makrygiannis G, Benetou V, Molina E, Donate Suarez I, Barricarte Gurrea A, Gonzalez CA, Tormo MJ, Altzibar JM, Olsen A, Tjonneland A, Gronbaek H, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Morois S, Slimani N, Boffetta P, Jenab M, Riboli E, Kaaks R (2010) Serum levels of IGF-I, IGFBP-3 and colorectal cancer risk: results from the EPIC cohort, plus a meta-analysis of prospective studies. Int J Cancer 126(7):1702–1715
27. Ahern TP, Hankinson SE, Willett WC, Pollak MN, Eliassen AH, Tamimi RM (2013) Plasma C-peptide, mammographic breast density, and risk of invasive breast cancer. Cancer Epidemiol Biomark Prev 22(10):1786–1796. doi:10.1158/1055-9965.EPI-13-0375
28. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, Li J, Ho GY, Xue X, Anderson GL, Kaplan RC, Harris TG, Howard BV, Wylie-Rosett J, Burk RD, Strickler HD (2009) Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl Cancer Inst 101(1):48–60. doi:10.1093/jnci/djn415
29. Kabat GC, Kim MY, Strickler HD, Shikany JM, Lane D, Luo J, Ning Y, Gunter MJ, Rohan TE (2012) A longitudinal study of serum insulin and glucose levels in relation to colorectal cancer risk among postmenopausal women. Br J Cancer 106(1):227–232. doi:10.1038/bjc.2011.512
30. Keinan-Boker L, Bueno De Mesquita HB, Kaaks R, Van Gils CH, Van Noord PA, Rinaldi S, Riboli E, Seidell JC, Grobbee DE, Peeters PH (2003) Circulating levels of insulin-like growth factor I, its binding proteins -1,-2, -3, C-peptide and risk of postmenopausal breast cancer. Int J Cancer 106(1):90–95. doi:10.1002/ijc.11193
31. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Manson JE, Li J, Harris TG, Rohan TE, Xue X, Ho GY, Einstein MH, Kaplan RC, Burk RD, Wylie-Rosett J, Pollak MN, Anderson G, Howard BV, Strickler HD (2008) A prospective evaluation of insulin and insulin-like growth factor-I as risk factors for endometrial cancer. Cancer Epidemiol Biomark Prev 17(4):921–929. doi:10.1158/1055-9965.EPI-07-2686
32. Wang Q, Bian CE, Peng H, He L, Zhao X (2015) Association of circulating insulin-like growth factor 1 and insulin-like growth factor binding protein 3 with the risk of ovarian cancer: a systematic review and meta-analysis. Mol Clin Oncol 3(3):623–628. doi:10.3892/mco.2015.516

33. Albanes D, Weinstein SJ, Wright ME, Mannisto S, Limburg PJ, Snyder K, Virtamo J (2009) Serum insulin, glucose, indices of insulin resistance, and risk of prostate cancer. J Natl Cancer Inst 101(18):1272–1279
34. Borugian MJ, Spinelli JJ, Sun Z, Kolonel LN, Oakley-Girvan I, Pollak MD, Whittemore AS, Wu AH, Gallagher RP (2008) Prostate cancer risk in relation to insulin-like growth factor (IGF)-I and IGF-binding protein-3: a prospective multiethnic study. Cancer Epidemiol Biomark Prev 17(1):252–254
35. Chen C, Lewis SK, Voigt L, Fitzpatrick A, Plymate SR, Weiss NS (2005) Prostate carcinoma incidence in relation to prediagnostic circulating levels of insulin-like growth factor I, insulin-like growth factor binding protein 3, and insulin. Cancer 103(1):76–84
36. Hubbard JS, Rohrmann S, Landis PK, Metter EJ, Muller DC, Andres R, Carter HB, Platz EA (2004) Association of prostate cancer risk with insulin, glucose, and anthropometry in the Baltimore longitudinal study of aging. Urology 63(2):253–258
37. Stattin P, Bylund A, Rinaldi S, Biessy C, Dechaud H, Stenman UH, Egevad L, Riboli E, Hallmans G, Kaaks R (2000) Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. J Natl Cancer Inst 92 (23):1910–1917
38. Stocks T, Lukanova A, Rinaldi S, Biessy C, Dossus L, Lindahl B, Hallmans G, Kaaks R, Stattin P (2007) Insulin resistance is inversely related to prostate cancer: a prospective study in Northern Sweden. Int J Cancer 120(12):2678–2686
39. Lai GY, Giovannucci EL, Pollak MN, Peskoe SB, Stampfer MJ, Willett WC, Platz EA (2014) Association of C-peptide and leptin with prostate cancer incidence in the health professionals follow-up study. Cancer Causes Control 25(5):625–632. doi:10.1007/s10552-014-0369-3
40. Roddam AW, Allen NE, Appleby P, Key TJ, Ferrucci L, Carter HB, Metter EJ, Chen C, Weiss NS, Fitzpatrick A, Hsing AW, Lacey JV Jr, Helzlsouer K, Rinaldi S, Riboli E, Kaaks R, Janssen JA, Wildhagen MF, Schroder FH, Platz EA, Pollak M, Giovannucci E, Schaefer C, Quesenberry CP Jr, Vogelman JH, Severi G, English DR, Giles GG, Stattin P, Hallmans G, Johansson M, Chan JM, Gann P, Oliver SE, Holly JM, Donovan J, Meyer F, Bairati I, Galan P (2008) Insulin-like growth factors, their binding proteins, and prostate cancer risk: analysis of individual patient data from 12 prospective studies. Ann Intern Med 149(7):461–471, W483–W468
41. Aleksandrova K, Boeing H, Nothlings U, Jenab M, Fedirko V, Kaaks R, Lukanova A, Trichopoulou A, Trichopoulos D, Boffetta P, Trepo E, Westhpal S, Duarte-Salles T, Stepien M, Overvad K, Tjonneland A, Halkjaer J, Boutron-Ruault MC, Dossus L, Racine A, Lagiou P, Bamia C, Benetou V, Agnoli C, Palli D, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita B, Peeters PH, Gram IT, Lund E, Weiderpass E, Quiros JR, Agudo A, Sanchez MJ, Gavrila D, Barricarte A, Dorronsoro M, Ohlsson B, Lindkvist B, Johansson A, Sund M, Khaw KT, Wareham N, Travis RC, Riboli E, Pischon T (2014) Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer. Hepatology 60(3):858–871. doi:10.1002/hep.27016
42. Nead KT, Sharp SJ, Thompson DJ, Painter JN, Savage DB, Semple RK, Barker A, Perry JR, Attia J, Dunning AM, Easton DF, Holliday E, Lotta LA, O'Mara T, McEvoy M, Pharoah PD, Scott RJ, Spurdle AB, Langenberg C, Wareham NJ, Scott RA (2015) Evidence of a causal association between insulinemia and endometrial cancer: a mendelian randomization analysis. J Natl Cancer Inst 107(9). doi:10.1093/jnci/djv178
43. Lukanova A, Lundin E, Micheli A, Arslan A, Ferrari P, Rinaldi S, Krogh V, Lenner P, Shore RE, Biessy C, Muti P, Riboli E, Koenig KL, Levitz M, Stattin P, Berrino F, Hallmans G, Kaaks R, Toniolo P, Zeleniuch-Jacquotte A (2004) Circulating levels of sex steroid hormones and risk of endometrial cancer in postmenopausal women. Int J Cancer 108 (3):425–432. doi:10.1002/ijc.11529
44. Kaaks R, Rinaldi S, Key TJ, Berrino F, Peeters PH, Biessy C, Dossus L, Lukanova A, Bingham S, Khaw KT, Allen NE, Bueno-de-Mesquita HB, van Gils CH, Grobbee D, Boeing H, Lahmann PH, Nagel G, Chang-Claude J, Clavel-Chapelon F, Fournier A,

Thiebaut A, Gonzalez CA, Quiros JR, Tormo MJ, Ardanaz E, Amiano P, Krogh V, Palli D, Panico S, Tumino R, Vineis P, Trichopoulou A, Kalapothaki V, Trichopoulos D, Ferrari P, Norat T, Saracci R, Riboli E (2005) Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. Endocr Relat Cancer 12(4):1071–1082. doi:10.1677/erc.1.01038

45. Key T, Appleby P, Barnes I, Reeves G (2002) Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 94(8):606–616
46. Kleinman D, Karas M, Danilenko M, Arbell A, Roberts CT, LeRoith D, Levy J, Sharoni Y (1996) Stimulation of endometrial cancer cell growth by tamoxifen is associated with increased insulin-like growth factor (IGF)-I induced tyrosine phosphorylation and reduction in IGF binding proteins. Endocrinology 137(3):1089–1095. doi:10.1210/endo.137.3.8603578
47. Kaaks R, Lukanova A, Kurzer MS (2002) Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomark Prev 11(12):1531–1543
48. Wild S, Pierpoint T, Jacobs H, McKeigue P (2000) Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. Hum Fertil (Camb) 3(2):101–105
49. Roddam AW, Allen NE, Appleby P, Key TJ (2008) Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst 100(3):170–183
50. Rinaldi S, Dossus L, Lukanova A, Peeters PH, Allen NE, Key T, Bingham S, Khaw KT, Trichopoulos D, Trichopoulou A, Oikonomou E, Pera G, Larranaga N, Martinez-Garcia C, Ardanaz E, Quiros JR, Tormo MJ, Tjonneland A, Olsen A, Overvad K, Chang-Claude J, Linseisen J, Schulz M, Boeing H, van Gils CH, Bueno-de-Mesquita BH, Pala V, Palli D, Panico S, Tumino R, Vineis P, Clavel-Chapelon F, Mesrine S, Boutron-Ruault MC, Lundin E, Agren A, Berglund G, Manjer J, Kumle M, Lund E, Slimani N, Saracci R, Riboli E, Kaaks R (2007) Endogenous androgens and risk of epithelial ovarian cancer: results from the European prospective investigation into cancer and nutrition (EPIC). Cancer Epidemiol Biomark Prev 16(1):23–29. doi:10.1158/1055-9965.EPI-06-0755
51. Lukanova A, Lundin E, Akhmedkhanov A, Micheli A, Rinaldi S, Zeleniuch-Jacquotte A, Lenner P, Muti P, Biessy C, Krogh V, Berrino F, Hallmans G, Riboli E, Kaaks R, Toniolo P (2003) Circulating levels of sex steroid hormones and risk of ovarian cancer. Int J Cancer 104 (5):636–642. doi:10.1002/ijc.10990
52. Chandran M, Phillips SA, Ciaraldi T, Henry RR (2003) Adiponectin: more than just another fat cell hormone? Diabetes Care 26(8):2442–2450
53. Stefan N, Vozarova B, Funahashi T, Matsuzawa Y, Weyer C, Lindsay RS, Youngren JF, Havel PJ, Pratley RE, Bogardus C, Tataranni PA (2002) Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. Diabetes 51 (6):1884–1888
54. Kim AY, Lee YS, Kim KH, Lee JH, Lee HK, Jang SH, Kim SE, Lee GY, Lee JW, Jung SA, Chung HY, Jeong S, Kim JB (2010) Adiponectin represses colon cancer cell proliferation via AdipoR1- and -R2-mediated AMPK activation. Mol Endocrinol 24(7):1441–1452. doi:10.1210/me.2009-0498
55. Aleksandrova K, Boeing H, Jenab M, Bueno-de-Mesquita HB, Jansen E, van Duijnhoven FJ, Fedirko V, Rinaldi S, Romieu I, Riboli E, Romaguera D, Westphal S, Overvad K, Tjonneland A, Boutron-Ruault MC, Clavel-Chapelon F, Kaaks R, Lukanova A, Trichopoulou A, Lagiou P, Trichopoulos D, Agnoli C, Mattiello A, Saieva C, Vineis P, Tumino R, Peeters PH, Arguelles M, Bonet C, Sanchez MJ, Dorronsoro M, Huerta JM, Barricarte A, Palmqvist R, Hallmans G, Khaw KT, Wareham N, Allen NE, Crowe FL, Pischon T (2012) Total and high-molecular weight adiponectin and risk of colorectal cancer: the European prospective investigation into cancer and nutrition study. Carcinogenesis 33 (6):1–8. doi:10.1093/carcin/bgs133

56. Song M, Zhang X, Wu K, Ogino S, Fuchs CS, Giovannucci EL, Chan AT (2013) Plasma adiponectin and soluble leptin receptor and risk of colorectal cancer: a prospective study. Cancer Prev Res 6(9):875–885. doi:10.1158/1940-6207.CAPR-13-0169
57. Xu XT, Xu Q, Tong JL, Zhu MM, Huang ML, Ran ZH, Xiao SD (2011) Meta-analysis: circulating adiponectin levels and risk of colorectal cancer and adenoma. J Dig Dis 12 (4):234–244. doi:10.1111/j.1751-2980.2011.00504.x
58. Yang X, Li J, Cai W, Yang Q, Lu Z, Yu J, Yu H, Zhang N, Sun D, Qu Y, Guo H, Wen F, Ji Y (2015) Adiponectin gene polymorphisms are associated with increased risk of colorectal cancer. Med Sci Monit Int Med J Exp Clin Res 21:2595–2606. doi:10.12659/MSM.893472
59. Song M, Gong J, Giovannucci EL, Berndt SI, Brenner H, Chang-Claude J, Curtis KR, Harrison TA, Hoffmeister M, Hsu L, Jiao S, Le Marchand L, Potter JD, Schoen RE, Seminara D, Slattery ML, White E, Wu K, Ogino S, Fuchs CS, Hunter DJ, Tworoger SS, Hu FB, Rimm E, Jensen M, Peters U, Chan AT (2014) Genetic variants of adiponectin and risk of colorectal cancer. Int J Cancer. doi:10.1002/ijc.29360
60. Gunter MJ, Wang T, Cushman M, Xue X, Wassertheil-Smoller S, Strickler HD, Rohan TE, Manson JE, McTiernan A, Kaplan RC, Scherer PE, Chlebowski RT, Snetselaar L, Wang D, Ho GY (2015) Circulating adipokines and inflammatory markers and postmenopausal breast cancer risk. J Natl Cancer Inst 107(9). doi:10.1093/jnci/djv169
61. Liao LM, Weinstein SJ, Pollak M, Li Z, Virtamo J, Albanes D, Chow WH, Purdue MP (2013) Prediagnostic circulating adipokine concentrations and risk of renal cell carcinoma in male smokers. Carcinogenesis 34(1):109–112. doi:10.1093/carcin/bgs322
62. Soliman PT, Cui X, Zhang Q, Hankinson SE, Lu KH (2011) Circulating adiponectin levels and risk of endometrial cancer: the prospective Nurses' Health Study. Am J Obstet Gynecol 204(2):167 e161–165. doi:10.1016/j.ajog.2010.08.045
63. Aleksandrova K, Boeing H, Nothlings U, Jenab M, Fedirko V, Kaaks R, Lukanova A, Trichopoulou A, Trichopoulos D, Boffetta P, Trepo E, Westhpal S, Duarte-Salles T, Stepien M, Overvad K, Tjonneland A, Halkjaer J, Boutron-Ruault MC, Dossus L, Racine A, Lagiou P, Bamia C, Benetou V, Agnoli C, Palli D, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita B, Peeters PH, Gram IT, Lund E, Weiderpass E, Quiros JR, Agudo A, Sanchez MJ, Gavrila D, Barricarte A, Dorronsoro M, Ohlsson B, Lindkvist B, Johansson A, Sund M, Khaw KT, Wareham N, Travis RC, Riboli E, Pischon T (2014) Inflammatory and metabolic biomarkers and risk of liver and bilary tract cancer. Hepatology. doi:10.1002/hep.27016
64. Michikawa T, Inoue M, Sawada N, Sasazuki S, Tanaka Y, Iwasaki M, Shimazu T, Yamaji T, Mizokami M, Tsugane S (2013) Plasma levels of adiponectin and primary liver cancer risk in middle-aged Japanese adults with hepatitis virus infection: a nested case-control study. Cancer Epidemiol Biomark Prev 22(12):2250–2257. doi:10.1158/1055-9965.EPI-13-0363
65. Nkontchou G, Bastard JP, Ziol M, Aout M, Cosson E, Ganne-Carrie N, Grando-Lemaire V, Roulot D, Capeau J, Trinchet JC, Vicaut E, Beaugrand M (2010) Insulin resistance, serum leptin, and adiponectin levels and outcomes of viral hepatitis C cirrhosis. J Hepatol 53 (5):827–833. doi:10.1016/j.jhep.2010.04.035
66. Bell L, Considine R (eds) (2006) Chapter 3: leptin and obesity. Leptin. Springer, New York
67. Slattery ML, Wolff RK (2007) Leptin and colorectal cancer: an undefined link. Nat Clin Pract Gastroenterol Hepatol 4(3):118–119. doi:10.1038/ncpgasthep0743
68. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM (1994) Positional cloning of the mouse obese gene and its human homologue. Nature 372(6505):425–432
69. Garofalo C, Surmacz E (2006) Leptin and cancer. J Cell Physiol 207(1):12–22. doi:10.1002/jcp.20472
70. Hardwick JC, Van Den Brink GR, Offerhaus GJ, Van Deventer SJ, Peppelenbosch MP (2001) Leptin is a growth factor for colonic epithelial cells. Gastroenterology 121(1):79–90
71. Stattin P, Palmqvist R, Soderberg S, Biessy C, Ardnor B, Hallmans G, Kaaks R, Olsson T (2003) Plasma leptin and colorectal cancer risk: a prospective study in Northern Sweden. Oncol Rep 10(6):2015–2021

72. Aleksandrova K, Boeing H, Jenab M, Bueno-de-Mesquita HB, Jansen E, van Duijnhoven FJ, Rinaldi S, Fedirko V, Romieu I, Riboli E, Gunter MJ, Westphal S, Overvad K, Tjonneland A, Halkjaer J, Racine A, Boutron-Ruault MC, Clavel-Chapelon F, Kaaks R, Lukanova A, Trichopoulou A, Lagiou P, Trichopoulos D, Mattiello A, Pala V, Palli D, Tumino R, Vineis P, Buckland G, Sanchez MJ, Amiano P, Huerta JM, Barricarte A, Menendez V, Peeters PH, Soderberg S, Palmqvist R, Allen NE, Crowe FL, Khaw KT, Wareham N, Pischon T (2012) Leptin and soluble leptin receptor in risk of colorectal cancer in the European prospective investigation into cancer and nutrition cohort. Cancer Res. doi:10.1158/0008-5472.CAN-12-0465
73. Stattin P, Lukanova A, Biessy C, Soderberg S, Palmqvist R, Kaaks R, Olsson T, Jellum E (2004) Obesity and colon cancer: does leptin provide a link? Int J Cancer 109(1):149–152. doi:10.1002/ijc.11668
74. Tamakoshi K, Toyoshima H, Wakai K, Kojima M, Suzuki K, Watanabe Y, Hayakawa N, Yatsuya H, Kondo T, Tokudome S, Hashimoto S, Suzuki S, Kawado M, Ozasa K, Ito Y, Tamakoshi A (2005) Leptin is associated with an increased female colorectal cancer risk: a nested case-control study in Japan. Oncology 68(4–6):454–461
75. Ho GY, Wang T, Gunter MJ, Strickler HD, Cushman M, Kaplan RC, Wassertheil-Smoller S, Xue X, Rajpathak SN, Chlebowski RT, Vitolins MZ, Scherer PE, Rohan TE (2012) Adipokines linking obesity with colorectal cancer risk in postmenopausal women. Cancer Res 72(12):3029–3037. doi:10.1158/0008-5472.CAN-11-2771
76. Joshi RK, Kim WJ, Lee SA (2014) Association between obesity-related adipokines and colorectal cancer: a case-control study and meta-analysis. World J Gastroenterol (WJG) 20 (24):7941–7949. doi:10.3748/wjg.v20.i24.7941
77. Partida-Perez M, de la Luz Ayala-Madrigal M, Peregrina-Sandoval J, Macias-Gomez N, Moreno-Ortiz J, Leal-Ugarte E, Cardenas-Meza M, Centeno-Flores M, Maciel-Gutierrez V, Cabrales E, Cervantes-Ortiz S, Gutierrez-Angulo M (2010) Association of LEP and ADIPOQ common variants with colorectal cancer in Mexican patients. Cancer Biomark (section A of Disease markers) 7(3):117–121. doi:10.3233/CBM-2010-0154
78. Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? Lancet 357 (9255):539–545. doi:10.1016/S0140-6736(00)04046-0
79. Jess T, Rungoe C, Peyrin-Biroulet L (2012) Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. Clin Gastroenterol Hepatol (The Official Clinical Practice Journal of the American Gastroenterological Association) 10(6):639–645. doi:10.1016/j.cgh.2012.01.010
80. Laukoetter MG, Mennigen R, Hannig CM, Osada N, Rijcken E, Vowinkel T, Krieglstein CF, Senninger N, Anthoni C, Bruewer M (2011) Intestinal cancer risk in Crohn's disease: a meta-analysis. J Gastrointest Surg (Official Journal of the Society for Surgery of the Alimentary Tract) 15(4):576–583. doi:10.1007/s11605-010-1402-9
81. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS (2005) Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA 294(8):914–923. doi:10.1001/jama.294.8.914
82. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Wu K, Fuchs CS (2008) Aspirin dose and duration of use and risk of colorectal cancer in men. Gastroenterology 134 (1):21–28. doi:10.1053/j.gastro.2007.09.035
83. Chan AT, Ogino S, Fuchs CS (2007) Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med 356(21):2131–2142. doi:10.1056/NEJMoa067208
84. Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, Chaussade S, Baron JA (2009) Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. J Natl Cancer Inst 101(4):256–266. doi:10.1093/jnci/djn485
85. Coussens LM, Werb Z (2002) Inflammation and cancer. Nature 420(6917):860–867. doi:10.1038/nature01322

86. Pendyala S, Neff LM, Suarez-Farinas M, Holt PR (2011) Diet-induced weight loss reduces colorectal inflammation: implications for colorectal carcinogenesis. Am J Clin Nutr 93 (2):234–242. doi:10.3945/ajcn.110.002683
87. Toriola AT, Cheng TY, Neuhouser ML, Wener MH, Zheng Y, Brown E, Miller JW, Song X, Beresford SA, Gunter MJ, Caudill MA, Ulrich CM (2012) Biomarkers of inflammation are associated with colorectal cancer risk in women but are not suitable as early detection markers. Int J Cancer. doi:10.1002/ijc.27942
88. Toriola AT, Ulrich CM (2011) Is there a potential use for C-reactive protein as a diagnostic and prognostic marker for colorectal cancer? Future Oncol 7(10):1125–1128. doi:10.2217/fon.11.92
89. Tsilidis KK, Branchini C, Guallar E, Helzlsouer KJ, Erlinger TP, Platz EA (2008) C-reactive protein and colorectal cancer risk: a systematic review of prospective studies. Int J Cancer 123 (5):1133–1140. doi:10.1002/ijc.23606
90. Aleksandrova K, Jenab M, Boeing H, Jansen E, Bueno-de-Mesquita HB, Rinaldi S, Riboli E, Overvad K, Dahm CC, Olsen A, Tjonneland A, Boutron-Ruault MC, Clavel-Chapelon F, Morois S, Palli D, Krogh V, Tumino R, Vineis P, Panico S, Kaaks R, Rohrmann S, Trichopoulou A, Lagiou P, Trichopoulos D, van Duijnhoven FJ, Leufkens AM, Peeters PH, Rodriguez L, Bonet C, Sanchez MJ, Dorronsoro M, Navarro C, Barricarte A, Palmqvist R, Hallmans G, Khaw KT, Wareham N, Allen NE, Spencer E, Romaguera D, Norat T, Pischon T (2010) Circulating C-reactive protein concentrations and risks of colon and rectal cancer: a nested case-control study within the European prospective investigation into cancer and nutrition. Am J Epidemiol 172(4):407–418. doi:10.1093/aje/kwq135
91. Nimptsch K, Aleksandrova K, Boeing H, Janke J, Lee YA, Jenab M, Bueno-de-Mesquita HB, Jansen EH, Tsilidis KK, Trichopoulou A, Weiderpass E, Wu C, Overvad K, Tjonneland A, Boutron-Ruault MC, Dossus L, Racine A, Kaaks R, Canzian F, Lagiou P, Trichopoulos D, Palli D, Agnoli C, Tumino R, Vineis P, Panico S, Johansson A, Van Guelpen B, Khaw KT, Wareham N, Peeters PH, Quiros JR, Vencesla Garcia A, Molina-Montes E, Dorronsoro M, Chirlaque MD, Barricarte Gurrea A, Key TJ, Duarte-Salles T, Stepien M, Gunter MJ, Riboli E, Pischon T (2015) Association of CRP genetic variants with blood concentrations of C-reactive protein and colorectal cancer risk. Int J Cancer 136(5):1181–1192. doi:10.1002/ijc.29086
92. Prizment AE, Folsom AR, Dreyfus J, Anderson KE, Visvanathan K, Joshu CE, Platz EA, Pankow JS (2013) Plasma C-reactive protein, genetic risk score, and risk of common cancers in the atherosclerosis risk in communities study. Cancer Causes Control 24(12):2077–2087. doi:10.1007/s10552-013-0285-y
93. Allin KH, Nordestgaard BG, Zacho J, Tybjaerg-Hansen A, Bojesen SE (2010) C-reactive protein and the risk of cancer: a mendelian randomization study. J Natl Cancer Inst 102 (3):202–206. doi:10.1093/jnci/djp459
94. Kakourou A, Koutsioumpa C, Lopez DS, Hoffman-Bolton J, Bradwin G, Rifai N, Helzlsouer KJ, Platz EA, Tsilidis KK (2015) Interleukin-6 and risk of colorectal cancer: results from the CLUE II cohort and a meta-analysis of prospective studies. Cancer Causes Control 26(10):1449–1460. doi:10.1007/s10552-015-0641-1