Insulin resistance and cancer: epidemiological evidence

Manami Inoue and Shoichiro Tsugane

Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

(Correspondence should be addressed to M Inoue; Email: mnminoue@ncc.go.jp)

Abstract

Epidemiological research into insulin resistance has focused on excess body weight, type 2 diabetes mellitus (DM), physical activity, and coffee consumption. These common modifiable factors have also been suggested to play a role in the process of carcinogenesis via associations with insulin resistance. Findings of systematic literature reviews and meta-analyses have generally supported an association between excess body weight and DM with an increased risk of colon cancer in males, and of liver, pancreatic, and endometrial cancers. Inverse relationships between these cancers and physical activity and coffee consumption have been shown, both of which are known to reduce the risk of DM. Interventions directed at or involving these variables should contribute to decreasing the risk of insulin resistance-associated cancer.

Endocrine-Related Cancer (2012) 19 F1–F8

Introduction

A substantial body of epidemiological evidence over recent decades has suggested a positive link between excess bodyweight and type 2 diabetes mellitus (DM) and many types of cancer. Studies have also suggested an inverse association between these cancers and physical activity and coffee consumption, both of which are suggested to decrease the risk of DM. These findings share the common keyword ‘insulin resistance’, and each factor plays a role in the carcinogenic process via this condition (Tsugane & Inoue 2010). Various recent systematic reviews and meta-analyses have helped establish the quantitative evaluation of these associations. Here, we review epidemiological evidence for the association between factors involved in insulin resistance and cancer risk, with a focus on the four factors commonly targeted in epidemiological research, namely excess body weight, DM, physical activity, and coffee consumption. Further, we summarize several possible mechanisms of insulin resistance-associated carcinogenesis.

Risk factors related to insulin resistance and cancer

Excess body weight and cancer risk

In its second report, the World Cancer Research Fund/American Institute for Cancer Research

(WCRF report 2007) assessed causal link between several factors and individual cancers using systematic reviews of epidemiological evidence, and also interpretations of relevant mechanisms and animal experimental data (WCRF/AICR 2007). This report states that excess body weight convincingly increases the risk of esophageal adenocarcinoma, colorectal cancer, pancreatic cancer, postmenopausal breast cancer, endometrial cancer, and kidney cancer. Further, it probably increases the risk of gallbladder cancer, and possibly increases the risk of liver cancer. The WCRF report also indicates that increased abdominal fatness, as assessed by waist circumference and/or waist–hip ratio, confers a convincing increase in the risk of colorectal cancer, as well as a probable increase in risk of pancreatic cancer, postmenopausal breast cancer, and endometrial cancer. As shown in Table 1, meta-analysis of a number of cohort studies from North America, Europe, Australia, and Asia-Pacific, with geometric mean follow-up periods from 8.4 years (breast cancer) to 14.4 years (multiple myeloma) (Renehan *et al.* 2008b), showed the magnitude of risk with a 5 kg/m² increase in body mass index (BMI) greater for esophageal adenocarcinoma (relative risk (RR)=1.5); and cancers of thyroid (RR=1.3), colon (RR=1.2), kidney (RR=1.2), and liver (RR=1.2) in men; and for endometrial cancer

Table 1 Summary results from recent meta-analyses of the association between factors related to insulin resistance and cancer risk

Cancer site	Excess body weight (per 5 kg/m ² increase of BMI)						Type 2 diabetes (diabetes vs nondiabetes)			Physical activity (highest vs lowest)			Coffee consumption (highest vs lowest)		
	Men			Women											
	SRR	(95% CI)	Number of studies (CH/CC)	SRR	(95% CI)	Number of studies (CH/CC)	Ref.	SRR	(95% CI)	Number of studies (CH/CC)	Ref.	SRR	(95% CI)	Number of studies (CH/CC)	Ref.
Oral pharynx	0.71	(0.60–0.85)	3	0.57	(0.47–0.69)	2	[1]	1.30	(1.12–1.50)	17 (11/6)	[2]	0.64	(0.51–0.80)	9 (1/8)	[19]
Esophageal squamous cell carcinoma	1.52	(1.33–1.74)	5	1.51	(1.31–1.74)	3	[1]	1.01	(0.90–1.11)	10 (10/0)	[3]	0.87	(0.65–1.17)	7 (1/6)	[19]
Esophageal adenocarcinoma	0.97	(0.88–1.06)	8	1.04	(0.90–1.20)	5	[1]	1.26	(1.20–1.31)	24 (16/8)	[4]	1.18	(0.81–1.71)	3 (0/3)	[19]
Stomach	1.24	(1.20–1.28)	22	1.09	(1.05–1.13)	19	[1]	2.31	(1.87–2.84)	49 (32/17)	[5]	0.90	(0.78–1.04)	11 (11/0)	[20]
Colorectum	1.09	(1.06–1.12)	18	1.02	(1.00–1.05)	14	[1]	1.43	(1.18–1.72)	21 (13/8)	[6]	0.98	(0.80–1.20)	10 (10/0)	[20]
Rectum	1.24	(0.95–1.62)	4	1.07	(1.00–2.08)	1	[1]	1.94	(1.66–2.27)	35 (35/0)	[7]	0.45	(0.38–0.53)	10 (4/6)	[21]
Liver	1.09	(0.99–1.21)	4	1.59	(1.02–2.47)	2	[1]	1.20	(1.12–1.28)	20 (15/5)	[8]	1.13	(0.99–1.29)	54 (17/37)	[22]
Biliary tract	1.07	(0.93–1.23)	12	1.12	(1.02–1.22)	11	[1]	1.20	(1.12–1.28)	20 (15/5)	[8]	1.27	(1.04–1.54)	13 (5/8)	[23]
Pancreas	0.76	(0.70–0.83)	11	0.80	(0.66–0.97)	6	[1]	1.20	(1.12–1.28)	20 (15/5)	[8]	0.95	(0.90–1.00)	18 (9/9)	[24]
Lung	1.17	(1.05–1.30)	6	0.96	(0.92–1.01)	5	[1]	1.20	(1.12–1.28)	20 (15/5)	[8]	0.95	(0.90–1.00)	18 (9/9)	[24]
Malignant melanoma	1.12	(1.08–1.16)	31				[1]								
Breast	0.92	(0.88–0.97)	20				[1]								
Postmenopausal breast	1.59	(1.50–1.68)	19				[1]								
Premenopausal breast	1.03	(0.99–1.08)	13				[1]								
Endometrium	1.03	(1.00–1.07)	27				[1]								
Ovary	1.24	(1.15–1.34)	11	1.34	(1.25–1.43)	12	[1]	2.10	(1.75–2.53)	16 (3/13)	[9]	0.81	(0.72–0.92)	13 (6/7)	[17]
Prostate	1.03	(1.00–1.07)	27				[1]					0.90	(0.84–0.95)	43 (19/24)	[18]
Kidney	1.33	(1.04–1.70)	4	1.14	(1.06–1.23)	3	[1]	0.84	(0.76–0.93)	19 (12/7)	[10]	1.16	(1.01–1.33)	12 (4/8)	[25]
Bladder	1.06	(1.03–1.09)	6	1.07	(1.00–1.14)	7	[1]	1.42	(1.08–1.42)	16 (9/7)	[11]	1.16	(1.01–1.33)	12 (4/8)	[26]
Thyroid	1.11	(1.05–1.18)	7	1.11	(1.07–1.15)	6	[1]	1.19	(1.04–1.35)	16 (5/11)	[12]				
Non-Hodgkin's lymphoma	1.08	(1.02–1.14)	7	1.17	(1.04–1.32)	7	[1]								
Multiple myeloma															
Leukemia															

Sources: Ref., references; [1] Renehan *et al.* (2008b), [2] Huang *et al.* (2008b), [3] Marimuthu *et al.* (2011), [4] Deng *et al.* (2012), [5] Wang *et al.* (2012), [6] Ren *et al.* (2011), [7] Ben *et al.* (2011), [8] Larsson *et al.* (2007), [9] Friberg *et al.* (2007), [10] Kasper & Giovannucci (2006), [11] Larsson & Wolk (2011), [12] Larsson *et al.* (2006), [13] Mitri *et al.* (2008), [14] Wolin *et al.* (2009), [15] O'Rourke *et al.* (2010), [16] Tardon *et al.* (2005), [17] Olsen *et al.* (2007), [18] Liu *et al.* (2011), [19] Turati *et al.* (2011), [20] Je *et al.* (2009), [21] Bravi *et al.* (2007), [22] Turati *et al.* (2012), [23] Tang *et al.* (2010), [24] Tang *et al.* (2009), [25] Je & Giovannucci (2011), [26] Park *et al.* (2010). Abbreviations: CC, case-control study; CH, cohort study; SRR, summary relative risk; 95%CI, 95% confidence interval.

(RR=1.6), gallbladder cancer (RR=1.6), esophageal adenocarcinoma (RR=1.5), and kidney cancer (RR=1.3) in women. A statistically significant sex difference has been observed for the risk of colon cancer, for which the RR was 1.1 in women. In that study, the duration of follow-up or the mean age at baseline had little effect on the positive association between BMI and cancer, and populations in the Asia-Pacific regions showed a stronger association with breast cancer, independently of menopausal status. Since then, two pooled analyses of over one million Caucasian (Berrington de Gonzalez *et al.* 2010) and Asian subjects (Zheng *et al.* 2011) reported an increased risk of cancer mortality with increased BMI in both white and East Asian populations, but not in Indian or Bangladeshi populations. No good explanation for this difference has appeared, but it is suggested that the lack of association in these two populations may be partly due to confounding by socioeconomic status; namely, subjects with a high BMI in less developed countries are more likely to have a high socioeconomic status and thus better access to health care.

In the United States, the population attributable fraction of excess body weight (BMI ≥ 25 kg/m²) has been estimated at 4% of male and 14% of female total cancer deaths (Calle *et al.* 2003), and in Europe at 3% of male and 4% of female total cancer incidence in 2002, and 3 and 9% in 2008 respectively (Renahan *et al.* 2010). In comparison, Japanese estimates for 2005 indicate that excess body weight was responsible for <1% of male and 1–2% of female cancer incidence and mortality (Inoue *et al.* 2011).

Type 2 DM and cancer risk

Accumulating epidemiological evidence over decades supports a positive link between DM and site-specific cancers in different populations, which are unrelated to excess body weight. Recent systematic reviews and meta-analyses in both Western and Asian populations showed a strong positive association for DM and pancreatic cancer (RR=1.8–1.9; Huxley *et al.* 2005, Ben *et al.* 2011), hepatocellular carcinoma (RR=2.3; Wang *et al.* 2012), and endometrial cancer (RR=2.1; Friberg *et al.* 2007), while weaker but nevertheless positive links were seen for kidney (RR=1.4; Larsson & Wolk 2011), biliary tract (RR=1.4; Ren *et al.* 2011), bladder (RR=1.2; Larsson *et al.* 2006), colorectal (RR=1.3; Deng *et al.* 2012), esophageal (RR=1.3; Huang *et al.* 2012), and breast cancers (RR=1.2; Larsson *et al.* 2007), and also non-Hodgkin's lymphoma (RR=1.2; Mitri *et al.* 2008). By comparison, an inverse association was reported for

prostate cancer (RR=0.8; Kasper & Giovannucci 2006; Table 1). Links with other types of cancer, less common than those consistently associated with DM, have been unclear due to limited evidence and have yet to be elucidated.

Possible mechanism for the link between excess body weight, DM, and cancer

The mechanism by which excess body weight increases cancer risk is possibly explained by insulin and insulin-like growth factor (IGF), sex steroids, and adipokines, which are connected through insulin (Calle & Kaaks 2004, Renahan *et al.* 2008a). Their roles might differ among cancer types.

A chronic excess body weight condition increases production of free fatty acids, cytokines such as tumor necrosis factor- α and interleukin 6, and leptin from adipose tissue, while it decreases adiponectin production, which together lead to the development of insulin resistance and chronic hyperinsulinemia (Calle & Kaaks 2004, Gallagher & LeRoith 2010). Chronic hyperinsulinemia decreases IGF-binding protein 1 (IGFBP1) and IGFBP2 concentrations in blood and other local tissues, which results in an increase in bioavailable free IGF1. Circulating total IGF1, a major element of free IGF1, increases the risk of colorectal, prostate, and premenopausal breast cancers. The sex difference in colorectal cancer risk might be partly explained by the higher concentration of circulating total IGF1 in men than in women (Juul *et al.* 1994, Renahan *et al.* 2008b).

The increased risk for breast cancer in postmenopausal women might be accounted for by the increased conversion of precursors of androgens to estradiol (E₂) via increased activity of aromatase enzyme in adipose tissue (Key & Verkasalo 1999). With regard to endometrial cancer, elevated E₂ leads to an increase in endometrial cell proliferation and inhibition of apoptosis (Graham & Clarke 1997, Calle & Kaaks 2004), simultaneously it also stimulates local IGF1 synthesis in the endometrium (Murphy 1994). Moreover, chronic hyperinsulinemia might promote carcinogenesis in tissues which are sensitive to estrogen by reducing sex-hormone-binding globulin concentrations in blood, as well as by increasing bioavailable estrogen (Calle & Kaaks 2004). In men, adiposity and testosterone concentration are inversely associated (Derby *et al.* 2006), whereas in women, they have a positive association (Key *et al.* 2003). This difference might explain sex differences in the association between BMI and cancer risk.

Adipokines are mainly produced from adipose tissue. The most abundant adipokines are leptin and adiponectin, which are implicated as mediators of the effects of obesity on cancer development. Leptin is secreted from adipocytes and involved in appetite control and energy metabolism. Circulating levels of this factor are high in obese conditions. Epidemiological studies suggest an association between circulating leptin levels and cancer progression, with the strongest link for colon, prostate, and breast cancers (Hursting & Berger 2010). Adiponectin is produced by adipocytes and involved in the regulation of carbohydrate and lipid metabolism, and insulin sensitivity. In contrast to other adipokines, plasma levels of adiponectin are decreased in response to several metabolic impairments, including DM, dyslipidemia, and extreme obesity. Plasma concentration of adiponectin shows an inverse association with excess body weight (Renahan *et al.* 2006), and levels are substantially higher in women than in men. The anti-angiogenic and anti-inflammatory activities of this agent may inhibit tumor growth (Barb *et al.* 2007).

While the association between DM and cancer differs among different cancer types, several mechanisms for the association have been hypothesized to date, such as the effect of hyperglycemia or insulin resistance and endogenous hyperinsulinemia (Giovannucci *et al.* 2010). In addition, excess body weight increases the risk of DM, which in the early stages is characterized by insulin resistance, followed by subsequent hyperinsulinemia (Tabak *et al.* 2009) before the development of hyperglycemia. Moreover, hyperinsulinemia may promote tumor cell growth directly via insulin receptors (Giovannucci *et al.* 2010). However, the association between DM and cancer may be partly due to shared risk factors between the two diseases, such as excess body weight, physical activity, smoking, and so on. Also, whether DM is associated with both cancer incidence and prognosis/mortality remains to be solved, and the answer may influence the screening and treatment strategies of both diseases.

Protective factors associated with insulin resistance and cancer

Physical activity and cancer risk

Substantial evidence supports an inverse association between physical activity and cancer risk at several sites, and physical activity is now regarded as an important cancer prevention target. The second WCRF/AICR report concluded that all types of physical activity (occupational, household, transport,

and recreational) convincingly decrease the risk of colon cancer, and probably also reduce the risk of postmenopausal breast cancer and endometrial cancer, either in association with excess body weight or independent of it (WCRF/AICR 2007). Evidence for a decrease in risk for lung, pancreatic, and premenopausal breast cancers is limited. Meta-analysis has been limited due to difficulty in harmonizing the physical activity measures used by each study. In contrast, several recent meta-analyses reported inverse associations between physical activity and colon (RR=0.8; Wolin *et al.* 2009), pancreas (RR=0.7; O'Rorke *et al.* 2010), lung (RR=0.7; Tardon *et al.* 2005), ovary (RR=0.8; Olsen *et al.* 2007), and prostate cancers (RR=0.9; Liu *et al.* 2011; Table 1). The recent systematic review with meta-analysis by Jeon *et al.* (2007) showed that regular physical activity of moderate intensity produced a substantial decrease in the risk of DM (RR=0.7) independently of excessive body weight.

A variety of mechanisms have been put forward to explain the association of physical activity for these cancers, including changes in insulin and IGF or sex hormones, immune modulation, alterations in free radical generation, and changes in body weight. Direct effects on these cancers have also been proposed (Lee 2003, Westerlind 2003). Exercise increases insulin sensitivity and reduces fasting insulin and C-peptide levels (Regensteiner *et al.* 1991), thereby improving insulin resistance. Physical activity appears to lower the levels of biologically available sex hormones, which could lead to decreased risk of hormone-related cancers such as the breast, endometrium, ovary, and prostate. Physical activity also induces increases in antitumor immune defenses by increasing the number and activity of macrophages, lymphokine-activated killer cells, and their regulating cytokines. Strenuous exercise increases the production of free radicals, whereas chronic exercise improves free radical defenses by upregulating the activities of free scavenger enzymes and antioxidant levels. Physical activity prevents cancer development through a reduction in abdominal fat mass (Friedenreich & Orenstein 2002). Overall, there appears to be a wide variety of potential mechanisms, and it is unknown to what degree the pathway between physical activity and cancer is attributable to insulin resistance. Also, even though physical activity has benefit in reducing the risk of cancer, an optimal level of physical activity to prevent or promote cancer remains to be elucidated. Nevertheless, it is reasonable to suggest that moderate but not strenuous physical activity potentially reduces the risk of cancer by improving insulin resistance.

Coffee consumption and cancer risk

The second WCRF/AICR report in 2007 (WCRF/AICR 2007) reviewed the association between coffee and risk for pancreatic and kidney cancers. While the effect of coffee on cancer risk remains controversial, many epidemiological studies have reported a strong protective effect in hepatocellular carcinoma and endometrial cancer (Arab 2010). A meta-analysis supported the association between coffee consumption and risk reduction in liver (RR=0.54; Bravi *et al.* 2007) and endometrial cancers (RR=0.71; Je & Giovannucci 2011; Table 1), while a borderline protective effect was also shown for colon cancer. This effect was stronger in women (RR=0.79) than in men (RR=1.00), particularly in Japanese populations (RR=0.62), although a plausible explanation for this sex difference deserves further investigation (Je *et al.* 2009). A recently large-scale prospective study in the US reported a null association for total cancer mortality (Freedman *et al.* 2012), which suggests that the effect of coffee varies by cancer site, likely depending on whether it is associated with insulin resistance or not.

The favorable effects of coffee intake on carcinogenesis are suggested to result from three predominant constituents, namely chlorogenic acid, caffeine, and diterpenes. Chlorogenic acid, a potent antioxidant and inhibitor of glucose-6-phosphate translocase in the liver, reduces gluconeogenesis and inflammation in the liver and the glucose absorption in the gut, which leads to an improvement in insulin resistance by elevating insulin sensitivity (Tunnicliffe & Shearer 2008). This effect may not be in conflict with the finding that higher coffee intake is related to lower postload glucose concentrations, rather than to fasting concentrations (van Dam *et al.* 2004, Yamaji *et al.* 2004). Like chlorogenic and caffeic acid, coffee diterpenes in coffee oil, such as cafestol and kahweol, might also decrease mutagenesis, tumorigenesis, and the genotoxicity of carcinogens, and also decrease DNA adduct formation.

Recent studies provide evidence that coffee has a protective effect against DM (van Dam & Hu 2005) and various cancers. Acute caffeine ingestion decreases glucose disposal (Greer *et al.* 2001, Keijzers *et al.* 2002, Lee *et al.* 2005). Meanwhile, US studies show that decaffeinated coffee decreases the risk of DM, and a cross-sectional analysis showed that coffee had a stronger inverse association with hyperglycemia than caffeine (Isogawa *et al.* 2003). Coffee constituents other than caffeine might thus also have favorable effects on DM. Perhaps, importantly, coffee is also rich in magnesium, which has known to improve insulin

sensitivity and insulin secretion (Larsson & Wolk 2007).

This large body of evidence, along with biological plausibility, indicates that coffee consumption has a protective effect against insulin resistance, and may decrease the risk of colon, liver, pancreatic and endometrial cancers associated with DM.

Conclusion

A substantial body of epidemiological evidence leaves little doubt that insulin resistance is an important factor in the development of cancer at various sites, including colon, liver, pancreas, and endometrium. The factors covered in this review – excess body weight, DM, physical activity, and coffee consumption – play a role in the carcinogenic process through their association with insulin resistance. Interventions based around these factors should accordingly help decrease the risk of insulin resistance-associated cancer.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

Funding

This work was supported by the National Cancer Center Research and Development Fund and by funds for the Third Term Comprehensive Control Research for Cancer from the Ministry of Health, Labour, and Welfare, Japan.

References

- Arab L 2010 Epidemiologic evidence on coffee and cancer. *Nutrition and Cancer* **62** 271–283. (doi:10.1080/01635580903407122)
- Barb D, Williams CJ, Neuwirth AK & Mantzoros CS 2007 Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. *American Journal of Clinical Nutrition* **86** s858–s866.
- Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, Zhang H & Li Z 2011 Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. *European Journal of Cancer* **47** 1928–1937. (doi:10.1016/j.ejca.2011.03.003)
- Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB *et al.* 2010 Body-mass index and mortality among 1.46 million white adults. *New England Journal of Medicine* **363** 2211–2219. (doi:10.1056/NEJMoa1000367)
- Bravi F, Bosetti C, Tavani A, Bagnardi V, Gallus S, Negri E, Franceschi S & La Vecchia C 2007 Coffee

- drinking and hepatocellular carcinoma risk: a meta-analysis. *Hepatology* **46** 430–435. (doi:10.1002/hep.21708)
- Calle EE & Kaaks R 2004 Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nature Reviews. Cancer* **4** 579–591. (doi:10.1038/nrc1408)
- Calle EE, Rodriguez C, Walker-Thurmond K & Thun MJ 2003 Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *New England Journal of Medicine* **348** 1625–1638. (doi:10.1056/NEJMoa021423)
- van Dam RM & Hu FB 2005 Coffee consumption and risk of type 2 diabetes: a systematic review. *Journal of the American Medical Association* **294** 97–104. (doi:10.1001/jama.294.1.97)
- van Dam RM, Dekker JM, Nijpels G, Stehouwer CD, Bouter LM & Heine RJ 2004 Coffee consumption and incidence of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes: the Hoorn Study. *Diabetologia* **47** 2152–2159. (doi:10.1007/s00125-004-1573-6)
- Deng L, Gui Z, Zhao L, Wang J & Shen L 2012 Diabetes mellitus and the incidence of colorectal cancer: an updated systematic review and meta-analysis. *Digestive Diseases and Sciences* **57** 1576–1585. (doi:10.1007/s10620-012-2055-1)
- Derby CA, Zilber S, Brambilla D, Morales KH & McKinlay JB 2006 Body mass index, waist circumference and waist to hip ratio and change in sex steroid hormones: the Massachusetts Male Ageing Study. *Clinical Endocrinology* **65** 125–131. (doi:10.1111/j.1365-2265.2006.02560.x)
- Freedman ND, Park Y, Abnet CC, Hollenbeck AR & Sinha R 2012 Association of coffee drinking with total and cause-specific mortality. *New England Journal of Medicine* **366** 1891–1904. (doi:10.1056/NEJMoa1112010)
- Friberg E, Orsini N, Mantzoros CS & Wolk A 2007 Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia* **50** 1365–1374. (doi:10.1007/s00125-007-0681-5)
- Friedenreich CM & Orenstein MR 2002 Physical activity and cancer prevention: etiologic evidence and biological mechanisms. *Journal of Nutrition* **132** 3456S–3464S.
- Gallagher EJ & LeRoith D 2010 Insulin, insulin resistance, obesity, and cancer. *Current Diabetes Reports* **10** 93–100. (doi:10.1007/s11892-010-0101-y)
- Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG & Yee D 2010 Diabetes and cancer: a consensus report. *Diabetes Care* **33** 1674–1685. (doi:10.2337/dc10-0666)
- Graham JD & Clarke CL 1997 Physiological action of progesterone in target tissues. *Endocrine Reviews* **18** 502–519. (doi:10.1210/er.18.4.502)
- Greer F, Hudson R, Ross R & Graham T 2001 Caffeine ingestion decreases glucose disposal during a hyperinsulinemic–euglycemic clamp in sedentary humans. *Diabetes* **50** 2349–2354. (doi:10.2337/diabetes.50.10.2349)
- Huang W, Ren H, Ben Q, Cai Q, Zhu W & Li Z 2012 Risk of esophageal cancer in diabetes mellitus: a meta-analysis of observational studies. *Cancer Causes & Control* **23** 263–272. (doi:10.1007/s10552-011-9874-9)
- Hursting SD & Berger NA 2010 Energy balance, host-related factors, and cancer progression. *Journal of Clinical Oncology* **28** 4058–4065. (doi:10.1200/JCO.2010.27.9935)
- Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F & Woodward M 2005 Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *British Journal of Cancer* **92** 2076–2083. (doi:10.1038/sj.bjc.6602619)
- Inoue M, Sawada N, Matsuda T, Iwasaki M, Sasazuki S, Shimazu T, Shibuya K & Tsugane S 2011 Attributable causes of cancer in Japan in 2005 – systematic assessment to estimate current burden of cancer attributable to known preventable risk factors in Japan. *Annals of Oncology* **23** 1362–1369. (doi:10.1093/annonc/mdr437)
- Isogawa A, Noda M, Takahashi Y, Kadowaki T & Tsugane S 2003 Coffee consumption and risk of type 2 diabetes mellitus. *Lancet* **361** 703–704. (doi:10.1016/S0140-6736(03)12586-X)
- Je Y & Giovannucci E 2011 Coffee consumption and risk of endometrial cancer: findings from a large up-to-date meta-analysis. *International Journal of Cancer* **131** 1700–1710. (doi:10.1002/ijc.27408)
- Je Y, Liu W & Giovannucci E 2009 Coffee consumption and risk of colorectal cancer: a systematic review and meta-analysis of prospective cohort studies. *International Journal of Cancer* **124** 1662–1668. (doi:10.1002/ijc.24124)
- Jeon CY, Lokken RP, Hu FB & van Dam RM 2007 Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. *Diabetes Care* **30** 744–752. (doi:10.2337/dc06-1842)
- Juul A, Bang P, Hertel NT, Main K, Dalgaard P, Jorgensen K, Muller J, Hall K & Skakkebaek NE 1994 Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. *Journal of Clinical Endocrinology and Metabolism* **78** 744–752. (doi:10.1210/jc.78.3.744)
- Kasper JS & Giovannucci E 2006 A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiology, Biomarkers & Prevention* **15** 2056–2062. (doi:10.1158/1055-9965.EPI-06-0410)
- Keijzers GB, De Galan BE, Tack CJ & Smits P 2002 Caffeine can decrease insulin sensitivity in humans. *Diabetes Care* **25** 364–369. (doi:10.2337/diacare.25.2.364)
- Key TJ & Verkasalo PK 1999 Endogenous hormones and the aetiology of breast cancer. *Breast Cancer Research* **1** 18–21. (doi:10.1186/bcr7)
- Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, Stanczyk FZ, Stephenson HE Jr, Falk RT, Miller R *et al.* 2003 Body mass index, serum sex

- hormones, and breast cancer risk in postmenopausal women. *Journal of the National Cancer Institute* **95** 1218–1226. (doi:10.1093/jnci/djg022)
- Larsson SC & Wolk A 2007 Magnesium intake and risk of type 2 diabetes: a meta-analysis. *Journal of Internal Medicine* **262** 208–214. (doi:10.1111/j.1365-2796.2007.01840.x)
- Larsson SC & Wolk A 2011 Diabetes mellitus and incidence of kidney cancer: a meta-analysis of cohort studies. *Diabetologia* **54** 1013–1018. (doi:10.1007/s00125-011-2051-6)
- Larsson SC, Orsini N, Brismar K & Wolk A 2006 Diabetes mellitus and risk of bladder cancer: a meta-analysis. *Diabetologia* **49** 2819–2823. (doi:10.1007/s00125-006-0468-0)
- Larsson SC, Mantzoros CS & Wolk A 2007 Diabetes mellitus and risk of breast cancer: a meta-analysis. *International Journal of Cancer* **121** 856–862. (doi:10.1002/ijc.22717)
- Lee IM 2003 Physical activity and cancer prevention – data from epidemiologic studies. *Medicine and Science in Sports and Exercise* **35** 1823–1827. (doi:10.1249/01.MSS.0000093620.27893.23)
- Lee S, Hudson R, Kilpatrick K, Graham TE & Ross R 2005 Caffeine ingestion is associated with reductions in glucose uptake independent of obesity and type 2 diabetes before and after exercise training. *Diabetes Care* **28** 566–572. (doi:10.2337/diacare.28.3.566)
- Liu Y, Hu F, Li D, Wang F, Zhu L, Chen W, Ge J, An R & Zhao Y 2011 Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. *European Urology* **60** 1029–1044. (doi:10.1016/j.eururo.2011.07.007)
- Marimuthu SP, Vijayaragavan P, Moysich KB & Jayaprakash V 2011 Diabetes mellitus and gastric carcinoma: Is there an association? *Journal of Carcinogenesis* **10** 30. (doi:10.4103/1477-3163.90481)
- Mitri J, Castillo J & Pittas AG 2008 Diabetes and risk of non-Hodgkin's lymphoma: a meta-analysis of observational studies. *Diabetes Care* **31** 2391–2397. (doi:10.2337/dc08-1034)
- Murphy LJ 1994 Growth factors and steroid hormone action in endometrial cancer. *Journal of Steroid Biochemistry and Molecular Biology* **48** 419–423. (doi:10.1016/0960-0760(94)90189-9)
- Olsen CM, Bain CJ, Jordan SJ, Nagle CM, Green AC, Whiteman DC & Webb PM 2007 Recreational physical activity and epithelial ovarian cancer: a case-control study, systematic review, and meta-analysis. *Cancer Epidemiology, Biomarkers & Prevention* **16** 2321–2330. (doi:10.1158/1055-9965.EPI-07-0566)
- O'Rorke MA, Cantwell MM, Cardwell CR, Mulholland HG & Murray LJ 2010 Can physical activity modulate pancreatic cancer risk? a systematic review and meta-analysis. *International Journal of Cancer* **126** 2957–2968.
- Park CH, Myung SK, Kim TY, Seo HG, Jeon YJ & Kim Y 2010 Coffee consumption and risk of prostate cancer: a meta-analysis of epidemiological studies. *BJU International* **106** 762–769. (doi:10.1111/j.1464-410X.2010.09493.x)
- Regensteiner JG, Mayer EJ, Shetterly SM, Eckel RH, Haskell WL, Marshall JA, Baxter J & Hamman RF 1991 Relationship between habitual physical activity and insulin levels among nondiabetic men and women. San Luis Valley Diabetes Study. *Diabetes Care* **14** 1066–1074.
- Ren HB, Yu T, Liu C & Li YQ 2011 Diabetes mellitus and increased risk of biliary tract cancer: systematic review and meta-analysis. *Cancer Causes & Control* **22** 837–847. (doi:10.1007/s10552-011-9754-3)
- Renahan AG, Frystyk J & Flyvbjerg A 2006 Obesity and cancer risk: the role of the insulin-IGF axis. *Trends in Endocrinology and Metabolism* **17** 328–336. (doi:10.1016/j.tem.2006.08.006)
- Renahan AG, Roberts DL & Dive C 2008a Obesity and cancer: pathophysiological and biological mechanisms. *Archives of Physiology and Biochemistry* **114** 71–83. (doi:10.1080/13813450801954303)
- Renahan AG, Tyson M, Egger M, Heller RF & Zwahlen M 2008b Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* **371** 569–578. (doi:10.1016/S0140-6736(08)60269-X)
- Renahan AG, Soerjomataram I, Tyson M, Egger M, Zwahlen M, Coebergh JW & Buchan I 2010 Incident cancer burden attributable to excess body mass index in 30 European countries. *International Journal of Cancer* **126** 692–702. (doi:10.1002/ijc.24803)
- Tabak AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimaki M & Witte DR 2009 Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. *Lancet* **373** 2215–2221. (doi:10.1016/S0140-6736(09)60619-X)
- Tang N, Zhou B, Wang B & Yu R 2009 Coffee consumption and risk of breast cancer: a metaanalysis. *American Journal of Obstetrics and Gynecology* **290** e291–e299.
- Tang N, Wu Y, Ma J, Wang B & Yu R 2010 Coffee consumption and risk of lung cancer: a meta-analysis. *Lung Cancer* **67** 17–22. (doi:10.1016/j.lungcan.2009.03.012)
- Tardon A, Lee WJ, Delgado-Rodriguez M, Dosemeci M, Albanes D, Hoover R & Blair A 2005 Leisure-time physical activity and lung cancer: a meta-analysis. *Cancer Causes & Control* **16** 389–397. (doi:10.1007/s10552-004-5026-9)
- Tsugane S & Inoue M 2010 Insulin resistance and cancer: epidemiological evidence. *Cancer Science* **101** 1073–1079. (doi:10.1111/j.1349-7006.2010.01521.x)
- Tunnicliffe JM & Shearer J 2008 Coffee, glucose homeostasis, and insulin resistance: physiological mechanisms and mediators. *Applied Physiology, Nutrition, and Metabolism* **33** 1290–1300. (doi:10.1139/H08-123)

- Turati F, Galeone C, La Vecchia C, Garavello W & Tavani A 2011 Coffee and cancers of the upper digestive and respiratory tracts: meta-analyses of observational studies. *Annals of Oncology* **22** 536–544. (doi:10.1093/annonc/mdq603)
- Turati F, Galeone C, Edefonti V, Ferraroni M, Lagiou P, La Vecchia C & Tavani A 2012 A meta-analysis of coffee consumption and pancreatic cancer. *Annals of Oncology* **23** 311–318. (doi:10.1093/annonc/mdr331)
- Wang P, Kang D, Cao W, Wang Y & Liu Z 2012 Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. *Diabetes/Metabolism Research and Reviews* **28** 109–122. (doi:10.1002/dmrr.1291)
- WCRF/AICR Ed 2007 *World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. Washington DC: AICR.
- Westerlind KC 2003 Physical activity and cancer prevention – mechanisms. *Medicine and Science in Sports and Exercise* **35** 1834–1840. (doi:10.1249/01.MSS.0000093619.37805.B7)
- Wolin KY, Yan Y, Colditz GA & Lee IM 2009 Physical activity and colon cancer prevention: a meta-analysis. *British Journal of Cancer* **100** 611–616. (doi:10.1038/sj.bjc.6604917)
- Yamaji T, Mizoue T, Tabata S, Ogawa S, Yamaguchi K, Shimizu E, Mineshita M & Kono S 2004 Coffee consumption and glucose tolerance status in middle-aged Japanese men. *Diabetologia* **47** 2145–2151. (doi:10.1007/s00125-004-1590-5)
- Zheng W, McLerran DF, Rolland B, Zhang X, Inoue M, Matsuo K, He J, Gupta PC, Ramadas K, Tsugane S *et al.* 2011 Association between body-mass index and risk of death in more than 1 million Asians. *New England Journal of Medicine* **364** 719–729. (doi:10.1056/NEJMoa1010679)

Received in final form 3 July 2012

Accepted 31 July 2012

Made available online as an Accepted Preprint
31 July 2012