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Insulin Resistance, Central Obesity and Risk of Colorectal Adenomas

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Abstract

Background—Increasing evidence supports insulin resistance (IR) as the underpinning of the obesity-colorectal neoplasia link. The homeostasis model assessment-IR (HOMA-IR) is a widely accepted index of evolving hyperinsulinemia and early IR. Studies of the relationship between HOMA-IR and colorectal adenomas are limited. Therefore, we sought to determine the associations of HOMA-IR and central obesity [waist-to-hip ratio (WHR)] with risk of colorectal adenomas in a screening colonoscopy-based study.

Methods—We have collected lifestyle information and fasting blood samples from 1,222 participants (320 incident adenoma cases and 902 without adenomas) prior to their screening colonoscopies. Unconditional logistic regression models were used to assess risk associations.

Results—In multivariate analysis of participants (n=1,093) reporting no anti-diabetic medication use, those in the top quartile of WHR were twice as likely (OR = 2.18, 95% CI = 1.33 – 3.57, p-trend = 0.003), and those in the top quartile of HOMA-IR were 63% more likely (OR = 1.63, 95% CI = 1.09 – 2.44, p-trend = 0.01), to have adenomas compared to those in the bottom quartiles. Stratified analysis revealed a statistically significant interaction between HOMA-IR and gender (p-interaction = 0.04) with the association largely limited to men: compared to those in the bottom tertile, men in the top tertile of HOMA-IR were twice more likely to have adenomas (OR = 2.11, 95% CI=1.18–3.78, p-trend=0.01).

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Conclusions—Our results support central obesity and insulin resistance, particularly in men, as important risk factors for the development of early colorectal neoplasia.

Keywords

colorectal adenomas; insulin resistance; central obesity; cross-sectional study

Background

Colorectal cancer (CRC) is the fourth most common cancer in both incidence and mortality.[1] Insulin resistance (IR), defined as a subnormal glycemic response to endogenous insulin, is characterized by compensatory hyperinsulinemia,[2] and has been positively associated with CRC.[3–5] There is also compelling evidence that obesity,[6] and accompanying hyperinsulinemia increase CRC risk.[7–9] An insulin-CRC hypothesis has been proposed to explain the observed association between obesity and CRC[3–4]; it suggests that accumulation of visceral fat is a strong determinant of IR and compensatory hyperinsulinemia,[10] which in turn promotes colorectal carcinogenesis.[2,11]

In agreement with the insulin-CRC hypothesis, elevated serum glucose and insulin, markers of IR, have been positively associated with CRC as well as colorectal adenomatous polyps, although published results have not been consistent.[12–16] Some studies,[12,17] but not all,[18] also suggest that the metabolic syndrome (MS), also known as IR syndrome, may be associated with increased risk of CRC and colorectal adenomas. Although some research suggests that the components of metabolic syndrome may appear to have an additive effect on colon neoplasia development acting through different pathophysiological pathways,[12] other data suggest that abdominal obesity is the one consistently associated with adenoma and CRC risk[19–21] and that increased waist circumference and components that capture impaired glucose tolerance, are the ones in fact related to CRC occurrence[19] and mortality.[22] These results are also supported by a recent study in animals showing that hyperinsulinemia, but not other components of this syndrome, seem to have a more direct role in CRC risk.[23–24]

The homeostasis model assessment of IR (HOMA-IR), an index calculated from the serum insulin and glucose values of an individual, has been suggested to provide an earlier indication of evolving hyperinsulinemia and/or hyperglycemia.[25] Studies of an association between HOMA-IR with CRC have in general yielded null results,[16,25–26] although results are still inconclusive.[27] For example, a case-cohort study of CRC among male smokers in the US found a higher risk of CRC in men from the highest HOMA-IR quartile as compared to those in the lowest quartile in age-adjusted analysis; but the observed association was reduced to non-significance after adjustment for additional covariates.[25] Meanwhile, a small case-control study in Turkey found an association between HOMA-IR and insulin with CRC risk and advanced CRC stage,[27] supporting the role of IR in the development of colorectal neoplasia. Although colorectal adenomatous polyps are well established precursor lesions for CRC,[28] results for an association between HOMA-IR and other markers of IR with polyps are limited and inconsistent.[8,16,29] To further elucidate the relationship of colorectal carcinogenesis with abdominal obesity and IR, we carried out a screening colonoscopy-based cross-sectional study of colorectal polyps. We hypothesized that both insulin resistance as measured by HOMA-IR and central obesity, as reflected by WHR, increase the risk of colorectal polyps.

Methods

Study Design and Study Population

In an ongoing screening colonoscopy-based cross-sectional study, known as the *Case Transdisciplinary Research in Cancer and Energetics [TREC] Colon Polyps Study*, we have prospectively collected data (lifestyle risk factors and fasting blood samples) from 1,259 individuals from January 2006 to March 2009. Patients were recruited from University Hospitals Case Medical Center and affiliated endoscopy centers and were eligible if they were scheduled for a routine screening colonoscopy; informed consent was obtained from each subject prior to their participation in the study. Individuals were determined to be ineligible if they had a prior diagnosis of cancer, colon polyps or inflammatory bowel disease (including Crohn's disease or ulcerative colitis), or were under the age of 30. After signing the informed consent, each participant was asked to complete a phone survey, fill out questionnaires and donate a blood sample. The phone survey was based on the lifestyle risk factor questionnaire (RFQ) developed by the NCI colon cancer family registry group (http://epi.grants.cancer.gov/CFR/about_questionnaires.html). The questionnaires each participant filled out included the Arizona Food Frequency Questionnaire, Physical Activity and Meat Preparation questionnaire. All three questionnaires were developed and validated by the Arizona Diet, Behavior and Quality of Life Assessment Center (http://azcc.arizona.edu/research/shared-services/bmss). A research nurse obtained the blood sample just prior to their colonoscopy and immediately refrigerated it. Blood processing was done the same day as collection. All tubes were spun for 15 minutes at 600g and aliquots of plasma, serum and concentrated buffy coat were prepared and frozen at −80°C. Incident cases were defined by histological confirmation of adenomatous polyps after their colonoscopy. We excluded individuals diagnosed with cancer. Patients who had a negative colonoscopy were classified as controls. The response rate was 64.9% among individuals eligible to participate in the study. The distribution of age, gender and race did not differ between individuals who participated and those who elected not to participate ($p>0.05$). This study has been approved by the University Hospitals Case Medical Center Institutional Review Board.

From these 1,259 participants who completed all the study procedures by the time of this analysis, 1 was excluded because of rectal cancer diagnosis. From these remaining 1,258, 2 were excluded because they were missing info on history of diabetes, 3 were missing information on diabetes medication use in the past 2 years and 31 had unreadable values of insulin/glucose. Thus, the final study population for this analysis included 1,222 individuals; 902 without adenomas (73.8%) and 320 with adenomas (26.2%).

Study variables

Information on relevant covariates was collected through a computer-assisted interview, a clinical visit and collection of biological specimens. Information on demographic characteristics included age, sex (men, women), race (Caucasian, African American, other), household income (<$15,000, $15,000–$29,000, $30,000–$44,000, $45,000–$69,000, ≥ $70,000) and family history of colorectal cancer (yes, no, unknown). Information on lifestyle characteristics included ever smoking (defined as consumption of at least one cigarette a day for 3 months or longer: yes, no), any alcohol consumption (defined as ever consumed alcohol at least once a week for 6 months or longer: yes, no) and non-steroidal anti-inflammatory drug (NSAID) use (defined as ever taken aspirin/ibuprofen at least twice a week for more than a month: yes, no). Anthropometric measurements included the measurement of the hip and waist of each participant (in inches), to calculate their waist to hip ratio (WHR). Weight and height were also measured to calculate BMI (kg/m^2). For women, menopausal status (pre and post-menopause) was defined according to self-reported

cessation of menses for 12 consecutive months or more, not due to pregnancy or medical treatment. Serum samples of participants were used to determine their fasting levels of insulin (μIU/mL) and glucose (mg/dL). HOMA-IR was defined according to the model proposed by Matthews[30] as (fasting plasma insulin in mU/l × fasting plasma glucose in mmol/l)/22.5. – Information on cases also included number (1, 2, 3+) and location of polyps (right, left and rectum).

Statistical analysis

Descriptive statistics (mean ± standard deviations and frequency distributions) were used to describe the demographic, lifestyle and clinical characteristics of persons with (n=320) and without adenomas (n=902); differences between cases and controls in the distribution of categorical and continuous variables were assessed with the use of chi-square statistics and Wilcoxon two-sided t-tests, respectively. The assumption of normal distribution of continuous variables was tested with the Shapiro-Wilk test for normality. Two-sided unconditional logistic regression models were used to assess the association between the main independent variables (insulin, glucose, HOMA-IR, BMI and WHR) and polyps. Quartiles of these variables were calculated from the distribution of these variables among controls not using diabetes medication, as medication use affects insulin and glucose levels. The variables insulin, glucose and HOMA-IR were studied in different models based on their calculated quartiles, all adjusting for relevant covariates and WHR as a continuous variable. The variables WHR and BMI were also evaluated independently in other models, after adjusting for relevant covariates and HOMA-IR as a continuous variable. P values for linear trend were calculated by treating categorical variables as continuous variables in multivariate logistic regression models. The use of HOMA-IR in subjects on insulin needs further validation, one of the reasons for this is the fact that exogenous (subcutaneously administered) insulin is not subject to the same degree of metabolism as endogenous insulin, and thus, the hepatic extraction assumptions included in the model used to calculate HOMA-IR do not apply when a subject is taking exogenous insulin.[31] Thus, logistic regression models in our study were also run excluding diabetes medication users (n=129). To explore the associations between WHR, BMI, HOMA-IR and polyps by gender, race and polyp location, stratified analyses for each of these variables were done (by sex, race and polyp location). As differences were only observed in the risk estimates when data were stratified by gender we tested for the statistical interaction of HOMA-IR (in quartiles) and gender in covariate adjusted multivariate logistic regression model using the likelihood ratio test. On gender stratified analysis, we used gender-specific tertiles (based on the distribution of controls with no current use of diabetes medication) to study the association of the main independent variables (insulin, glucose, HOMA-IR, BMI and WHR) with polyps. All statistical tests were 2-sided at $\alpha = 0.05$.

Results

Bivariate analysis

Table 1 compares the descriptive characteristics of persons with and without adenomatous polyps. Polyp distribution differed by age and sex; 33.1% of men and 21.9% of women had polyps ($p<0.0001$), while mean age was 57.8 ±8.2 years for persons with polyps as compared to 54.4±8.9 years for those without polyps ($p<0.0001$). A higher proportion of smokers (30.1%) had polyps as compared to non-smokers (21.6%); a higher proportion of persons with polyps was also observed among persons with the lowest level of household income (<$15,000) (34.8%) ($p=0.0007$). Higher mean values of insulin (8.21±7.7, $p=0.0013$), glucose (91.4±27.4, $p=0.0077$), HOMA-IR (1.9±2.0, $p=0.0013$), WHR (0.94± 0.09, $p<0.0001$) and waist circumference (40.25±7.05, $p=0.0004$) was also observed among persons with polyps as compared to their counterparts. No significant differences were

observed in the distribution of polyps by race, family history of colorectal cancer, NSAID use or alcohol consumption or in the mean values of hip circumference and BMI. Among persons with polyps (n=320), 64% had polyps in the right colon, 40% in the left and 15% in the rectum; whereas 74% had 1 polyp, 15% had 2 polyps and 11% had 3 or more (data not shown).

Multivariate analysis

Our initial analysis considered the complete study population (n=1,222); here, we assigned diabetes medication users to the fourth quartile of insulin, glucose and HOMA-IR. In these analyses, we found no significant association between insulin, glucose or HOMA-IR with polyps, after adjusting for age, sex, race, WHR, family history, income, NSAID, smoking and alcohol (Table 2). Nonetheless, we did see a significant trend with WHR, where those from the third and fourth quartiles were more likely to have polyps when compared to those from the lowest WHR quartile (p-trend<0.0001). Similar results were observed for BMI (Table 2).

Because HOMA-IR may not reflect the underlying insulin resistance status among patients taking insulin or other anti-diabetic medications,[31] we next excluded those patients and limited our multivariate analysis to persons not using diabetes medication (n=1,093). We found that both WHR and HOMA-IR were statistically significantly associated with risk of adenoma. Persons in the 4th quartile of HOMA-IR were 65% more likely to have polyps than those in the 1st quartile, and persons in the 3rd and 4th quartiles of WHR were twice as likely to have polyps than those in the 1st quartile (Table 2). When stratified by gender (main independent variables classified into tertiles due to small numbers), the association between HOMA-IR and polyps remained statistically significant for men, but not for women, and test for interaction was statistically significant (p for interaction = 0.0386) (Table 3). In men, those in the highest tertile were twice more likely to have polyps than those in the lowest tertile (OR = 2.03, 95% CI=1.08-3.80, p-trend=0.027). In women, further adjustment for or stratification by menopausal status did not change the results (data not shown). Meanwhile, although significant associations (p<0.05) were seen between WHR and adenomas in both men and women, significant trends between WHR tertiles and adenomas were observed only among women. On the contrary, significant trends between BMI tertiles and adenomas were seen only among men; no association was seen among women (Table 3). In addition, although no significant trends were observed between glucose tertiles and adenomas for either men or women, we also saw a significant positive trend in the association between insulin and adenomas only among men. Stratified analysis by ethnicity did not reveal appreciable differences between African American and Caucasian patients in the studied associations (data not shown).

Discussion

This cross-sectional study mounts to the growing evidence supporting an association between IR and WHR and colorectal adenomas. In multivariate analysis of participants reporting no anti-diabetic medication use, those in the top quartile of WHR were twice as likely to have adenomas compared to those in the bottom quartile. Also, stratified analysis revealed a statistically significant interaction between HOMA-IR and gender, with the association largely limited to men; compared to those in the bottom tertile of HOMA-IR, men in the top tertile were twice more likely to have adenomas.

It is well known that obesity is associated with risk of CRC in men; while in women there is an apparently more complex relationship between BMI and CRC; which may be the result of potentially complex interactions between insulin, IGF-1 and estrogen.[32] Many have suggested that WHR is a better measure of central obesity which may measure visceral fat

better than subcutaneous fat mass,[9–33] as visceral fat is very bioactive in generating adipokines, inflammation, oxidative stress, and IR.[2,33] Our results for an association between WHR and colon adenomas are consistent with numerous epidemiological studies that have shown positive associations between abdominal obesity and/or overweight/obesity and risk of CRC.[5,6,8,29,34] The strongest empirical support for mechanisms that link obesity and cancer risk involves the metabolic and endocrine effects of obesity, and the alterations they induce in production of peptide and steroid hormones including insulin, free IGF-1, insulin-like growth factor binding protein-1 (IGFBP-1), insulin-like growth factor binding protein-3 (IGFBP-3), sex-hormone binding proteins and potentially adipocytokines secreted by adipose tissue (leptin, adiponectin, resistin, and the tumor necrosis factor).[5,33]

We only saw a significant association between HOMA-IR and adenomas for men, but not for women. In men, HOMA-IR is associated with colorectal polyps independent of WHR. In contrast, HOMA-IR reduced to non-significance when WHR was included in the model, suggesting that HOMA-IR contributes little information beyond central obesity in women. Our results for men are consistent with a previous Japanese study showing that the HOMA-IR index and visceral fat accumulation are associated with colorectal adenoma,[8] and also in line with a smaller study of patients with acromegaly showing association between hyperinsulinemia, IR and hyperplastic polyps and adenomas in the colon.[35] In this latter study, fasting insulin level and HOMA-IR were positively associated with the number of hyperplastic polyps and adenomas.[35] Meanwhile, our result of no association for women is consistent with a case-control study among men and women in Korea that found no differences in HOMA-IR between the adenoma and control group; similar to that study, we found that WHR was the most important independent risk factor for colon adenoma.[29] Although another small case-control study also found overall higher levels of insulin and HOMA-IR in CRC patients as compared to controls,[27] another one found similar null results for CRC risk and proposed that the neoplastic process in the colon might not be associated with hyperinsulinaemia or IR, but with pancreatic B-cell dysfunction typical of the early stages of diabetes.[26] Our null results for women are consistent with a study among postmenopausal women which saw that adjusting for waist circumference weakened the association of insulin and HOMA-IR with CRC risk[36] and with the lack of association of MS with colorectal adenomas in women as compared to men seen in various studies.[13,17–18] It's been hypothesized that the protective effects of estrogen or progesterone on the colon may be masking the true effects of MS on colorectal malignancies.[17,36] This is supported by a recent study in mice that has shown that estrogen can block the stimulatory effects of insulin in tumor progression and whose results support that the female reproductive system modulates obesity-induced IR, influencing CRC progression.[37]

Although HOMA-IR seems to be a better marker of IR,[25] studies have also looked at the association of other markers of IR with CRC and adenoma risk. Even though these studies have been somewhat inconsistent,[15] elevated insulin and glucose have shown a positive association with adenoma risk and decreased apoptosis in normal rectal mucosa; suggesting that insulin may act early in the adenoma-carcinoma sequence to promote the development of colorectal polyps by decreasing apoptosis in the normal mucosa.[14] Meanwhile, a study in Japan suggests that visceral adipose accumulation and makers of IR (insulin, glucose and HOMA-IR) are positively associated with the development of early-stage cancer but not colorectal adenomas.[16] Markers of IR (increased insulin and glucose) have also been associated with increased risk of adenoma recurrence,[13] and for those with increased glucose, the increase in risk for recurrence of advanced adenomas is even greater. In our study, we found a significant trend between increasing insulin tertiles and adenoma risk among men, but not among women; meanwhile, no clear association between fasting glucose and adenomas was observed for either men or women.

To date ours is the largest study of the relationship of HOMA-IR and colon adenomas. The fact that none of these previous studies stratified their analyses by gender may explain some of the inconsistencies in the results between ours and previous studies. Overall, results from our study support the IR-CRC hypothesis showing that IR is associated with the development of early colon neoplasia, especially in men. However, given the appreciable gender differences in the association between HOMA-IR, fasting insulin and colorectal adenomas, future studies should try to elucidate the biological reasons for these differences. These gender differences are of particular relevance as abdominal fat accumulation, and not insulin or HOMA-IR, has been associated with other hormone dependent conditions in women, such as oligomenorrhea[38]; suggesting a direct role of central adiposity on certain health conditions in women, independent of hyperinsulinemia and IR. Sedjo and colleagues[6] have suggested that obesity could influence the risk of colorectal polyps and carcinogenesis in 2 ways: 1) as obesity influences insulin status, it may increase disease risk through the role of insulin and IGF, or 2) it may contribute to other pathways, independent of the insulin pathway. For example, the hormones secreted by adipose tissue may play a role in the development and progression of polyps and/or CRC not only through their effect on IR but also by directly controlling cell proliferation.[16] Thus, an alternative pathway and potential hypothesis could be that sex differences observed in our study regarding the IR-colorectal adenomas association may be explained by differences in the secretion and/or interaction of adipocytokines and/or sex-hormones secreted by adipose tissue between men and women, which may influence a difference cascade of events between genders. In addition, given that the association between some of the studied parameters and disease status may also be influenced by other hormonal and reproductive characteristics of women (i.e. parity, menopausal status, exogenous hormone use),[24,39–40] these future studies should consider the impact and potential interactions of IR markers and these variables in colorectal adenoma risk among women.

A limitation of our study is that we only have information of serum levels of relevant biomarkers at the time of patient recruitment. Thus, these values may not adequately reflect the levels of these biomarkers over time and limits our ability to elucidate the temporal relationship between IR and development of colorectal adenomas. Among the strengths of this study is the fact that we recruited incident cases of CRC; thus, reducing the potential for recall bias in this group. In addition, the potential for misclassification bias was reduced as information on serum biomarkers was taken during fasting and anthropometric measurements were taken by trained nurses. In addition, an interviewer administered questionnaire provided us with information on relevant confounding variables.

In conclusion, results from our screening colonoscopy-based incident cross-sectional study of adenoma support the hypothesis that IR and central obesity promote the development of early colorectal neoplasia. Our study highlights that fact that therapeutics or chemoprevention targeting IR may represent a novel avenue for CRC prevention. Indeed, a recent 4-week clinical randomized trial reported that a low dose of metformin, an anti-diabetic medication, significantly reduced the mean number of aberrant crypt fossi (ACF), supporting its potential use as a CRC chemopreventive agent in the future.[41] Furthermore, a practical implication of our study is that patients with IR are at increased risk of developing CRC and screening and early detection shall be emphasized.

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Table 1

Characteristics of cases and controls participating in the Case TREC Polyp Study Population (n=1,222).

	Polyps		Chi-square/T-test
	No (n=902)	Yes (n=320)	p-value
	No. (%)	No. (%)	
Sex			<0.0001
Male	313 (66.9)	155 (33.12)	
Female	589 (78.1)	165 (21.9)	
Race			0.21
Caucasian	558 (75.6)	180 (24.4)	
African American	323 (71.0)	132 (29.0)	
Other	21 (72.4)	8 (27.6)	
Income			0.01
< $15,000	118 (65.2)	63 (34.8)	
$15,000–$29,000	116 (74.8)	39 (25.2)	
$30,000–$44,000	109 (73.2)	40 (26.9)	
$45,000–$69,000	159 (80.7)	38 (19.3)	
≥$70,000	345 (72.8)	129 (27.2)	
Unknown	55 (83.3)	11 (16.7)	
Family history colorectal cancer			0.71
Yes	217 (75.6)	70 (24.4)	
No	665 (73.3)	242 (26.7)	
Unknown	20 (71.4)	8 (28.6)	
Ever Smoking			0.0007
Yes	462 (69.9)	199 (30.1)	
No	440 (78.4)	121 (21.6)	
NSAID[n]			0.52
Yes	427 (72.9)	159 (27.1)	
No	464 (74.5)	159 (25.5)	
Any Alcohol[‡]			0.37
Yes	593 (73.1)	218 (26.9)	
No	308 (75.5)	100 (24.5)	
	μ±SD	μ±SD	
Age, years	54.41±8.91	57.75 ±8.15	<0.0001*
Insulin, μIU/mL	7.25± 9.39	8.21 ± 7.73	0.0013*
Glucose, mg/dL	88.49± 29.73	91.43± 27.40	0.01*
HOMA-IR	1.78 ± 3.23	1.94 ±2.00	0.0004*
WHR [†]	0.91 ±0.09	0.94± 0.09	<0.0001*
BMI, kg/m^2 [‡‡]	29.37±6.96	30.30±7.43	0.44*
Waist, inches[††]	38.60±6.72	40.25±7.05	0.0004*

	Polyps		Chi-square/T-test
	No (n=902)	Yes (n=320)	p-value
	No. (%)	No. (%)	
Hip, inches†	42.38±6.08	42.63±6.06	0.49*

*Wilcoxon two-sample t-test p-value

Missing values:

n n=13,

‡ n=3,

† n=6,

†† n=5,

‡‡ n=1.

SD indicates standard deviations, NSAID indicates non-steroidal anti-inflammatory drug (NSAID), HOMA-IR indicates homeostasis model assessment-insulin resistance, WHR indicates waist-to-hip-ratio (WHR), BMI indicates body mass index.

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Table 2

Logistic regression models of the association between insulin resistance and polyps.

	Complete study population † (n=1222)				Population not using diabetes medication (n=1093)			
	OR (95% CI)	**p-trend**	**OR (95% CI)**	**p-trend**	**OR (95% CI)**	**p-trend**	**OR (95% CI)**	**p-trend**
Glucose		0.23		0.46		0.29		0.51
Q1	1.00*		1.00**		1.00*		1.00**	
Q2	1.81 (1.19–2.74)		1.70 (1.11–2.60)		1.76 (1.15–2.69)		1.63 (1.05–2.51)	
Q3	1.12 (0.73–1.71)		1.07 (0.70–1.66)		1.07 (0.70–1.66)		1.01 (0.65–1.57)	
Q4	1.54 (1.04–2.29)		1.41 (0.94–2.14)		1.56 (1.02–2.38)		1.42 (0.92–2.21)	
Insulin		0.03		0.07		0.03		0.06
Q1	1.00*		1.00**		1.00*		1.00**	
Q2	1.01 (0.68–1.50)		0.99 (0.66–1.49)		1.02 (0.67–1.54)		1.02 (0.67–1.55)	
Q3	1.22 (0.83–1.80)		1.17 (0.79–1.74)		1.30 (0.87–1.95)		1.22 (0.80–1.84)	
Q4	1.45 (0.99–2.12)		1.40 (0.94–2.08)		1.48 (0.99–2.21)		1.45 (0.95–2.21)	
HOMA-IR		0.04		0.10		0.01		0.02
Q1	1.00*		1.00**		1.00*		1.00**	
Q2	1.07 (0.70–1.63)		1.07 (0.69–1.66)		1.07 (0.70–1.64)		1.09 (0.70–1.68)	
Q3	1.21 (0.80–1.84)		1.14 (0.74–1.75)		1.23 (0.81–1.86)		1.16 (0.75–1.78)	
Q4	1.44 (0.98–2.11)		1.38 (0.92–2.06)		1.63 (1.09–2.44)		1.63 (1.07–2.50)	
WHR		<0.0001		<0.0001		<0.01		<0.01
Q1	1.00*		1.00***		1.00*		1.00***	
Q2	1.07 (0.67–1.71)		1.09 (0.68–1.74)		1.03 (0.64–1.65)		1.04 (0.64–1.68)	
Q3	1.80 (1.17–2.78)		1.92 (1.23–3.00)		1.85 (1.18–2.90)		1.96 (1.24–3.12)	
Q4	2.19 (1.39–3.43)		2.32 (1.45–3.69)		2.11 (1.31–3.39)		2.18 (1.33–3.57)	
BMI		0.06		0.03		0.02		0.02
Q1	1.00*		1.00***		1.00*		1.00***	
Q2	0.94 (0.62–1.41)		1.00 (0.66–1.51)		1.02 (0.67–1.55)		1.09 (0.71–1.67)	
Q3	1.08 (0.73–1.60)		1.15 (0.77–1.71)		1.21 (0.80–1.82)		1.29 (0.84–1.98)	
Q4	1.38 (0.94–2.02)		1.51 (1.01–2.27)		1.54 (1.02–2.33)		1.63 (1.05–2.52)	

* Model adjusted for age, sex and race.

** Model adjusted for age, sex, race, WHR (continuous variable), family history, income, NSAIDs, smoking and alcohol.

*** Model adjusted for age, sex, race, HOMA-IR (continuous variable), family history, income, NSAIDs, smoking and alcohol.

† Diabetes medication users assigned to 4th quartiles.

OR indicates odds ratio, HOMA-IR indicates homeostasis model assessment-insulin resistance, WHR indicates waist-to-hip-ratio, BMI indicates body mass index.

Table 3

Logistic regression models of the association between insulin resistance and polyps among persons not using diabetes medication, by sex (n=1,093).

	Women				Men			
	OR (95% CI)	**p-trend**	**OR (95% CI)**	**p-trend**	**OR (95% CI)**	**p-trend**	**OR (95% CI)**	**p-trend**
HOMA-IR		0.91		0.82		0.02		0.01
Q1	1.00*		1.00**		1.00*		1.00**	
Q2	0.88 (0.55–1.41)		0.82 (0.50–1.33)		1.69 (0.99–2.87)		1.74 (0.99–3.07)	
Q3	1.02 (0.63–1.65)		0.94 (0.56–1.56)		1.91 (1.12–3.29)		2.11 (1.18–3.78)	
WHR		0.01		0.01		0.07		0.10
Q1	1.00*		1.00***		1.00*		1.00***	
Q2	0.96 (0.59–1.58)		0.99 (0.60–1.63)		2.14 (1.25–3.65)		2.14 (1.23–3.71)	
Q3	1.83 (1.13–2.97)		1.92 (1.16–3.18)		1.69 (0.98–2.90)		1.64 (0.93–2.90)	
BMI		0.55		0.40		<0.01		0.02
Q1	1.00*		1.00***		1.00*		1.00***	
Q2	1.12 (0.70–1.79)		1.21 (0.75–1.96)		2.25 (1.31–3.87)		2.32 (1.31–4.09)	
Q3	1.16 (0.71–1.89)		1.25 (0.74–2.11)		2.31 (1.34–3.98)	2	.07 (1.13–3.77)	

* Adjusted for age and race.

** Adjusted for age, race, WHR (continuous variable), family history, income, NSAIDs, smoking and alcohol.

*** Adjusted for age, sex, race, homair as continuous variable, family history, income, nsaid, smoking and alcohol.

OR indicates odds ratio, HOMA-IR indicates homeostasis model assessment-insulin resistance, WHR indicates waist-to-hip-ratio, BMI indicates body mass index.