Definitions of the Insulin Resistance Syndrome

The 1st World Congress on the Insulin Resistance Syndrome

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This is the second of two articles covering the 1st World Congress on the Insulin Resistance Syndrome, which was held in Los Angeles, 21–22 November 2003.

The Adult Treatment Panel III: metabolic syndrome

Richard Pasternak (Boston, MA) discussed the deliberations that led the National Cholesterol Education Program Adult Treatment Panel (ATP) III to propose a new definition of the metabolic syndrome (1) and the impact of this proposal in heightening awareness of the insulin resistance syndrome (IRS). Coronary heart disease (CHD) is the main cause of death in the developed world, and Pasternak noted that contrary to general perceptions, malignancy is only approximately half as frequent a cause of mortality as CHD among women. The concept of metabolic syndrome extends in a precise way an important subset of patients at high risk for CHD. The definition was created to be clinically practical, evidence based, and applicable to existing datasets. The ATP did not find adequate evidence to recommend routine measurement of insulin sensitivity or of inflammatory markers. The 2-h glucose was not included because it was similarly felt not to add sufficient numbers of persons to justify the additional effort involved. The panel has been criticized for not calling the metabolic syndrome a CHD equivalent, but Pasternak pointed out that at that time there was no evidence that this was the case. Rather, the presence of the metabolic syndrome was felt to accentuate the risk accompanying elevated LDL cholesterol, mediated through existing and emerging risk factors. Clinical trials show evidence for modification of atherogenic dyslipidemia, blood pressure, and the prothrombotic state (with aspirin, which the panel recommended only for persons with CHD but which Pasternak suggested is appropriate for all persons with the syndrome) in persons undergoing LDL-lowering therapy. The primary management strategy should be to reverse its root causes of obesity and physical inactivity, with an option to intensify LDL lowering. It is notable that metabolic syndrome is particularly likely to be present in younger persons with CHD (2). With modification of the definition, metabolic syndrome is present in ~10% of children. Pasternak stated that analysis of the Atherosclerosis Risk in Communities study shows that 52% of persons with but 23% of those without metabolic syndrome have increased carotid intima-media thickness (IMT). Analysis of the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) trial suggests that the metabolic syndrome identifies a group among those with existing CHD that has greater absolute benefit from lipid-lowering treatment. Pasternak concluded by noting the association of C-reactive protein with atherosclerotic risk in the West of Scotland Coronary Prevention study, with additive effect to the presence of metabolic syndrome (3). In answer to a subsequent question, he also noted the usefulness of measurement of the ankle-brachial systolic pressure ratio for risk estimation.

The American Association of Clinical Endocrinologists: IRS

Daniel Einhorn (San Diego, CA) gave a similar assessment of the American Association of Clinical Endocrinologists (AACE) consensus definition of the IRS (4). Differences from the ATP III included focus on the IRS rather than on CVD, a decision to specifically exclude persons with type 2 diabetes, and recognition of the limitations of the fasting glucose and the usefulness of the 2-h postchallenge glucose in assessing insulin resistance. The number of associated conditions was expanded, and the use of a specific number of components to “diagnose” the syndrome was not considered appropriate; the IRS was felt to be a continuum of risk based on the number and severity of components. Cut points and numerical criteria were considered compromises to allow better assessment rather than ideal measures. The rationale for early recognition of the IRS includes the advantage of early and more aggressive lifestyle intervention, with closer and more focused medical follow-up and the potential benefit of identification of family members at risk. Close follow-up will allow treatment of individual components of the syndrome when cut points are crossed, particularly as the possibility of pharmacologic treatment of the syndrome is now being more widely entertained.

Obesity, based on either BMI or waist circumference, was seen as a risk factor rather than a criterion for the syndrome, since many obese persons do not have the syndrome and many with the syndrome are not obese. Measures of obesity must be ethnically based, and one must recognize that in certain Asian populations, both BMI and waist circumference criteria must be reduced by 15–20%. Other factors increasing the likelihood of the IRS include CVD, hypertension, polycystic ovary syndrome (PCOS), nonalcoholic fatty liver disease, or acanthosis nigricans;
non-Caucasian ethnicity; sedentary lifestyle; age >40 years; a history of gestational diabetes or glucose intolerance; or a family history of type 2 diabetes, hypertension, or CVD. All persons with such characteristics should have a measure of glycemia (including fasting and 2-h post-75-g oral glucose load), HDL cholesterol, and triglyceride. Tests not included were homeostasis model assessment, microalbumin, C-reactive protein, postchallenge lipids, brachial artery reactivity, plasminogen activator inhibitor 1, and leptin. The importance of PCOS, nonalcoholic fatty liver disease, pediatric aspects of metabolic syndrome, and the relationship of certain malignancies to the IRS (although data on this remain lacking) were also addressed. Hemodynamic factors, including increased sympathetic nervous system activity, prothrombotic factors, markers of inflammation, endothelial dysfunction, and hyperuricemia, may be additional components of the IRS.

There is controversy as to treatment targets for the IRS. The Diabetes Prevention Program targets for weight loss (≥7% of body wt) and fitness (≥150 min of physical activity per week) (5) are appropriate. Suggested CVD risk targets were LDL <100 mg/dl, triglyceride <150 mg/dl, and blood pressure <130/80 mmHg. Restriction of total and in particular of refined carbohydrates appeared useful. Aspirin, low-dose niacin, folate, and having a low threshold for administration of ACE inhibitors/angiotensin receptor blockers appeared reasonable. It is uncertain whether metformin and thiazolidinediones are appropriate for persons with the IRS. Statins, fibrates, high-dose niacin, and weight loss agents did not appear to be specifically indicated for the IRS, and it was recommended that they only be used for their specific indications.

Table 1—Definitions of the metabolic syndrome

<table>
<thead>
<tr>
<th>ATP III metabolic syndrome definition</th>
<th>At least three of the following criteria</th>
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<tr>
<td>waist circumference &gt;102 cm in men and &gt;88 cm in women</td>
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<tr>
<td>Serum triglycerides ≥150 mg/dl</td>
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<tr>
<td>HDL cholesterol &lt;40 mg/dl in men and &lt;50 mg/dl in women</td>
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<tr>
<td>Blood pressure ≥130/85 mmHg</td>
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<td>Serum glucose ≥110 mg/dl</td>
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<th>WHO metabolic syndrome definition</th>
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<tr>
<td>Diabetes, IGF, IGT, or HOMA insulin resistant and at least two of the following criteria</td>
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<tr>
<td>Waist-to-hip ratio &gt;0.90 in men or &gt;0.85 in women</td>
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<tr>
<td>Serum triglycerides ≥150 mg/dl or HDL cholesterol &lt;35 mg/dl in men and &lt;39 mg/dl in women</td>
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<tr>
<td>Urinary albumin excretion rate &gt;20 µg/min</td>
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<td>Blood pressure ≥140/90 mmHg</td>
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<th>AACE IRS definition</th>
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<tr>
<td>Presence of at least one of the following factors</td>
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<tr>
<td>Diagnosis of CVD, hypertension, PCOS, NAFLD, or acanthosis nigricans</td>
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<tr>
<td>Family history of type 2 diabetes, hypertension, or CVD</td>
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<tr>
<td>History of gestational diabetes or glucose intolerance</td>
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<tr>
<td>Non-Caucasian ethnicity</td>
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<tr>
<td>Sedentary lifestyle</td>
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<tr>
<td>BMI &gt;125.0 kg/m² and/or waist circumference &gt;40 in in men and &gt;35 in in women</td>
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<tr>
<td>Age &gt;40 years</td>
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<tr>
<td>and at least two of the following criteria</td>
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<tr>
<td>Triglycerides &gt;150 mg/dl</td>
</tr>
<tr>
<td>HDL cholesterol &lt;40 mg/dl in men and &lt;50 mg/dl in women</td>
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<tr>
<td>Blood pressure &gt;130/85 mmHg</td>
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<tr>
<td>Fasting glucose 110-125 mg/dl or 120-min postglucose challenge 140-200 mg/dl</td>
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<td>(diabetes is excluded from the AACE IRS)</td>
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<tr>
<th>EGIR IRS definition</th>
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<tr>
<td>Fasting hyperinsulinemia (highest 25%) and at least two of the following criteria</td>
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<tr>
<td>Fasting plasma glucose ≥6.1 mmol/l (excluding diabetes)</td>
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<tr>
<td>Blood pressure ≥140/90 mmHg or treated for hypertension</td>
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<tr>
<td>Triglycerides &gt;2.0 mmol/l or HDL cholesterol &lt;1.0 mmol/l or treated for dyslipidemia</td>
</tr>
<tr>
<td>Waist circumference ≥94 cm in men and ≥80 cm in women</td>
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A number of prospective studies have examined the relationship between the metabolic syndrome and CVD. In 1,209 Finnish men aged 42–60 years, the 10-year CVD risk was increased 2.1- and 2.5-fold with the ATP III and WHO IRS definitions, respectively (10). In the Botnia study, there was a 1.8-fold increase in risk in persons satisfying the WHO IRS criteria (11). Dekker presented analysis of the Hoorn study of 2,484 persons, begun in 1989 with persons then aged 50–75 years. Among 618 men and 750 women, after excluding those with diabetes, a history of CVD, or not permitting access to hospital records, there were 131 CVD deaths and 309 nonfatal CVD events through 2000. Of men and women, those with ATP III IRS were more likely to have hypertension, hypertriglyceridemia, low HDL cholesterol, and higher glucose, insulin, and waist circumference. Nineteen and 26% of men and women, respectively, in the study had IRS by the ATP III criteria, 32 and 17% by the WHO criteria, 19 and 26% by the EGIR criteria, and 35 and 33% by the AACE criteria, with 60–80% agreement among the various definitions. Dekker commented that >80% of persons in the population had high risk based on the AACE criterion (if one included the characteristic of sedentary lifestyle, she noted, the prevalence would be >95%). Among men, those having IRS according to either the ATP III or AACE criteria had a doubling of risk, while those with IRS according to the WHO and EGIR had a 1.5-fold increased risk. Among women, the associations were less strong. Subjects with IRS by the ATP III criteria had twice the risk of CVD without an increase in fatal CVD, and those satisfying

The IRS and CVD

Jacqueline Dekker (Amsterdam, the Netherlands) presented new findings of the Hoorn Study on the relationship between the IRS and CVD. High insulin predicts CVD in the general population (6), and factor analysis suggests that the IRS predicts CVD (7). A variety of working definitions of the IRS have been proposed. Those of the World Health Organization (WHO) (8), National Cholesterol Education Program ATP III (1), American College of Endocrinology (4), and European Group for the Study of Insulin Resistance (EGIR) (9) are shown in Table 1.

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the ACE criteria had double the risk of nonfatal CVD and a 1.5-fold increase in fatal CVD. The strengths of association were weaker for the WHO and EGIR criteria. In line with this, Dekker suggested that the IRS is associated with nonfatal CVD in women and fatal CVD in men and that the ATP III criteria are slightly better at predicting risk than those of the WHO, EGIR, and AACE.

Dekker raised the question of whether one should regard the IRS as a specific entity, noting that in models including individual risk factors as well as the syndrome, individual risk factors were better predictors of CVD than the presence of the IRS, regardless of which definition was used. Persons considered at “high risk” based on the AACE guidelines who did not have risk factors did not in fact have increased CVD risk, while risk increased with the number of positive risk factors, particularly among women. Other studies have shown the IRS not to be an independent predictor if individual risk factors were included in the analysis (12). In the WOSCOPS (West of Scotland Coronary Prevention Study), the ATP III IRS was associated with a 1.8-fold increase in CHD risk, but after adjusting for other risk factors, a more modest 1.3-fold increase was observed (3). Markers of inflammation, which are not included in the current IRS definitions, were also important risk factors in this analysis.

Using the Hoorn Study data, among men, high insulin predicted a 1.5-fold increase in CVD, increased waist circumference predicted a doubling, and hypertension predicted a two- to threefold increase in risk. Among women, high insulin and waist circumference predicted risk of nonfatal but not fatal CVD, and both low HDL and high triglyceride were significant factors predicting both total and fatal CVD. Other authors have noted that IRS, defined by both the ATP III and WHO criteria, was associated with CVD and increased carotid IMT (13,14).

The IRS and hypertension

Gerald Reaven discussed the relationship of the IRS to hypertension and CVD. In 1966, Welborn first investigated the interrelationship between hyperinsulinemia and hypertension, based on Australian data (15). In the 1980s, the finding of insulin resistance in persons with hypertension was reported by Ferran-nini, Reaven, and others, with subsequent evidence of hyperinsulinemia among first-degree relatives independent of overall and visceral obesity. Blood pressure levels are as strongly associated with insulin levels as with insulin resistance, as assessed by clamp technique (16). Using factor analysis, insulin levels are associated more strongly with dyslipidemia than with blood pressure, which has led to the notion that blood pressure is not as strongly related to insulin resistance. Reaven suggested that this may be explained by the heterogeneity of causes of essential hypertension. Reaven showed studies comparing persons with normal and increased blood pressure, suggesting a bimodal distribution of insulin levels among the latter group, with 50% of the hypertensive patients but 10% of those with normal blood pressure having evidence of hyperinsulinemia. He noted that insulin is a vasodilator and that acute insulin administration does not increase blood pressure levels, although the consequences of sustained endogenous hyperinsulinemia may be rather different. Insulin does cause sodium retention, and Reaven noted that insulin resistance at the level of skeletal muscle is not associated with renal insulin resistance to urate re-absorption; therefore, in the presence of insulin resistance, hyperinsulinemia may also lead to increased total body sodium. In a study comparing low- and high-sodium diets, atrial natriuretic peptide increased, plasma renin activity decreased, aldosterone decreased, and urinary nitric oxide (NO) showed a trend to increase with high-sodium diet, the impact of which was associated with the degree of insulin sensitivity. There was a negative correlation between the increase in blood pressure and the change in urinary NO, suggesting that the blood pressure increase among persons with insulin resistance is related to the inability of these individuals to compensate for the degree of sodium retention by increasing NO levels (17). The greater impact of blood pressure lowering on stroke than on CHD may, Reaven commented, be related to the heterogeneity of insulin sensitivity in hypertension, so that insulin-resistant hypertensive persons with hypertriglyceridemia and low HDL may have less benefit from blood pressure lowering alone. In a study from his group comparing persons with hypertension and normal versus ischemic change on electrocardiogram, the latter group showed evidence of insulin resistance, with hyperinsulinemia during a glucose tolerance test and lower HDL levels (18).

Association between the IRS and the PCOS

John E. Nestler (Richmond, VA) discussed the clinical implications of the association between insulin resistance and the PCOS. PCOS may be the most common endocrinopathy among young women and is a syndrome of chronic anovulation and hyperandrogenism that affects 6–10% of women of childbearing age and accounts for ~50–60% of female infertility due to anovulation. Most if not all of these women have insulin resistance. Insulin resistance plays a crucial role in the pathogenesis of the disorder, and weight loss through diet and exercise or use of insulin-sensitizing agents, including metformin, thiazolidinediones, and D-chiro-inositol, decreases androgens and improves ovulation. In a Cochrane meta-analysis (19), metformin monotherapy improved the ovulation rate 3.9-fold over placebo and the combination of metformin and clomiphene improved both the ovulation and pregnancy rates 4.4-fold compared with clomiphene alone. Nestler noted that in nonobese women with PCOS but with normal insulin sensitivity based on fasting and postglucose insulin levels, metformin and rosiglitazone each increased the likelihood of ovulation, further suggesting the importance of insulin resistance in the syndrome and the benefit of this treatment. A collaborative National Institutes of Health trial is being carried out in PCOS; it will compare clomiphene, metformin, and the combination not only in pregnancy induction but also in decreasing multiple gestations. Nestler noted that PCOS is associated with a 30–50% rate of early pregnancy loss and that hyperinsulinemia is also a risk factor for miscarriage. Women with early pregnancy loss have a low level of glycodelin, which has immunomodulatory effects protecting the developing fetus, and of IGF binding protein (IGFBP)-1. Use of metformin increased levels of both factors, suggesting that this agent might be effective during pregnancy (20). In assessment of 68 women treated with metformin during pregnancy versus 31 not treated, early pregnancy loss was 6/68 vs. 13/31 (21). The optimal timing of such treatment is uncertain, and it may be sufficient to re-
ceive metformin just at the time of conception.

General health risks for women with PCOS may be affected by their insulin resistance. Women with PCOS have 30 and 10% prevalence of impaired glucose tolerance and diabetes, respectively (22), and in the Nurses’ Health Study (NHS) of 101,073 women followed for 8 years, oligomenorrheic women had a twofold higher rate of conversion to type 2 diabetes (23). Conversely, 25–28% of women with type 2 diabetes have evidence of PCOS (24), and 80% of women with type 2 diabetes may have polycystic ovaries (25).

Beginning at age 45 years, women with PCOS have increased carotid IMT (26) and there is evidence of increased CHD event rates. Retrospective study of Swedish women who had ovarian wedge resection in the 1950s showed a 7.4-fold risk of myocardial infarction (27), and women having cardiac catheterization show an association between polycystic ovaries on ultrasound and the extent of coronary artery disease (28). Finally, Nestler noted, in the NHS, women with irregular menses had a doubled risk of fatal myocardial infarction. “This is not an infertility disorder alone,” he said, “it is a systemic disorder with long-term consequences.” These women should therefore have assessment of glucose tolerance, blood pressure, lipids, and other CVD risk factors. Goals of treatment are to improve reproductive function, decrease androgens (which may decrease risk of malignancy), and improve long-term risk. Nestler noted that oral contraceptives decrease endometrial cancer, decrease androgens, and have some benefit in decreasing hirsutism and acne, but he suggested that insulin sensitizers may have equal benefit in decreasing cancer and be equally beneficial in decreasing androgens and hirsutism. Furthermore, oral contraceptives may worsen insulin sensitivity (29), cause glucose intolerance (30,31), increase triglyceride levels, and increase CVD risk. In the NHS, 2,265 women followed for 12 years showed a 10% increase in type 2 diabetes risk with oral contraceptive treatment. Nestler reported that a recent meta-analysis of the CVD risk of oral contraceptive treatment suggests a two- to fourfold increased risk of myocardial infarction, although noting that the absolute risk is low in a general population of young women. In contrast, he suggested, insulin sensitizers may decrease CVD risk; therefore, these appear to be the preferred agents for long-term treatment.

The IRS in childhood

Alan Sinaiko (Minneapolis, MN) discussed the IRS in childhood, pointing out that “the roots of the syndrome go back into childhood.” Body weight among school-age children has increased progressively over the past decade, in association with a 1-to 2-mmHg blood pressure increase. Furthermore, there is evidence of target organ damage already existing in childhood, with obesity associated with abnormal flow-mediated vasodilation among 8- to 9-year-old children suggesting endothelial dysfunction. There is evidence of association of risk factors with fatty streaks and fibrous plaques in the coronary arteries among children dying during adolescence (32). Type 2 diabetes is increasing in children, suggesting that “not only are children fatter but they’re starting to present with the real disease” (33). Abnormal glucose tolerance is frequently seen among obese children, although it is noteworthy that fasting glucose is rarely abnormal (34), suggesting the need to perform glucose tolerance testing. In Sinaiko’s studies, there is strong correlation among BMI at ages 8, 13, and 25 years; therefore, it is incorrect to advise parents not to concern themselves with overweight children or that children usually lose weight as they grow older. Familial influences are also very important, with heritability analysis showing significant correlation between parents and children in both weight and insulin sensitivity. Puberty is associated with insulin resistance, and body size changes dramatically, with greater increase in body fat in girls and lean body mass in boys. Boys show a particular decrease in insulin sensitivity during adolescence.

Using the ATP III criteria, the prevalence of metabolic syndrome was 2, 4, and 8% at ages 13, 15, and 19, respectively. Sinaiko suggested that these criteria may underestimate the prevalence of the IRS among children, with better cutoffs for 110 mg/dl triglyceride, 40 mg/dl HDL (for both girls and boys), the 90th percentile for waist circumference, 110 mg/dl fasting glucose, and 120/68 mmHg blood pressure for boys and 110/70 for girls (35). In a study of 295 15-year-old children, comparing those with BMI above and below the median, insulin sensitivity was similar for both groups but blood pressure, triglyceride, and fasting insulin were higher and HDL cholesterol lower for the heavier children. Alternatively, dividing the groups by insulin sensitivity, fasting insulin, triglyceride, and HDL showed significant difference, with BMI being similar. Dividing into four groups based on BMI and insulin sensitivity above and below the median, fasting insulin, triglyceride, and systolic blood pressure increase in the heavy insulin-resistant group and HDL cholesterol decreases. The heavy insulin-resistant children had higher and the thinner insulin sensitive lower “Z-scores” for risk factor clusters of systolic blood pressure, triglyceride, HDL, and fasting insulin, “so there is something about being both insulin resistant and overweight.” Blood pressure showed strong clustering with the other risk factors. An important question is whether treatment should be recommended in childhood, and, if so, what approaches should be used.

The IRS and malignancy

Cell biological considerations. George Fantus (Toronto, Canada) discussed aspects of the link between insulin resistance, hyperinsulinemia, and cancer. Obesity contributes to 14 and 20% of cancer deaths in men and in women, with a particular increase in risk of colon and rectal, stomach, pancreas, and liver cancers in men and ovary, non-Hodgkin’s lymphoma, breast, uterine, and liver cancers in women (36). A number of studies have bolstered the evidence of association of breast cancer with hyperinsulinemia (37,38) and diabetes (39–41). In animal studies, induction of diabetes with streptozotocin slows mammary tumor growth, suggesting insulin to be a required growth factor. Normal mammary epithelial cells express insulin receptors, which are increased in breast cancer cells. Overexpression of insulin receptors in normal breast epithelial cells results in a transformed phenotype. Insulin is a known mitogen for cultured breast cancer cells, and can act via the IGF-I receptor, insulin receptor, and hybrid receptors, all of which are expressed by breast tumors. In addition, insulin augments the growth response of mammary tumor cells to other growth factors, such as IGF-I, and both insulin and IGF-I augment growth and
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cell-cycle progression in response to estrogen.

Fantus pointed out that the IGF-II receptor is not a tyrosine kinase but a mannos-6-phosphate receptor and may have protective effects in carcinogenesis. At a 10-nmol/l level, not binding to the IGF-1 receptor, insulin activates a number of breast cancer cell lines. Insulin receptor levels appear to be upregulated in tumors of transgenic mice with increased breast cancer risk. In some breast cancer cell lines, IGF-II has similar potency to insulin in stimulating autophosphorylation of the insulin receptor, perhaps because of overexpression of the IGF-1 receptor in these cells. There are two isoforms of the insulin receptor, IR-A lacking the exon 11 found in IR-B. IR-A is the major fetal insulin receptor in most tissues and is overexpressed in breast tumors. Insulin and IGF-II both bind and signal via IR-A (42). In mice not expressing the IGF-1 receptor, with addition of IR-A, IR-B, and IGF-1 receptor, insulin particularly activates the insulin receptors, whereas IGF-II particularly activates IR-A and the IGF-1 receptor. IGF-II appears to have a greater mitogenic than metabolic potency, whereas insulin has greater metabolic potency, although it is not clear what underlies the differences in the subsequent intracellular signals. Fantus noted that there are hybrid IR-A/IGF-1 and IR-B/IGF-1 receptors; the IR-B hybrid shows less potent insulin binding, and both hybrids show greater IGF-1 and IGF-II binding. An important additional factor (which will not be apparent on measuring of plasma insulin levels) may be local breast cancer cell production of IGF-1 and IGF-II with autocrine effects.

Insulin may act indirectly, modulating IGF-I and/or IGFBPs, increasing IGF-1 and decreasing IGFBP-1 and -3, which sequester IGF-1 and have cellular actions, with IGFBP-1 binding to the fibroblast receptor, IGFBP-3 acting at the transforming growth factor-β receptor and inhibiting growth, and IGFBPs possibly acting to release IGFs at specific cellular sites (43,44). Insulin may also enhance the mitogenic actions of other growth factors, perhaps increasing IR-A and hybrid A by downregulating IR-B and possibly acting via farnesylation to change growth patterns. Insulin priming of growth factor stimulated mitogenesis should then be blocked by a farnesyl transferase inhibitor, and indeed such an effect is demonstrable (45). In breast cancer cells, the farnesylation pathway appears to have growth promoting action (46). Finally, insulin may increase estrogen action by increasing bioavailable estrogen due to a decrease in sex hormone-binding globulin, by influencing estrogen receptors, and by increasing aromatization of androgen to estrogen at the tissue level, a phenomenon which has been demonstrated in breast tissue. It is also important that estrogen upregulates the IGF-1 receptor and IGFBP-1 and -2 and may directly activate the IGF-1 receptor, thereby increasing insulin signaling.

Life-style and insulin resistance in cancer. Rowan Chlebowski (Los Angeles, CA) discussed lifestyle factors, such as obesity, caloric intake, and physical activity (47,48), that may affect insulin resistance in cancer. Meta-analysis has shown a 1.56-fold increase in breast cancer associated with obesity (49). Increased estradiol has been shown to be associated with breast cancer (50) and, along with increased estrone, testosterone, androsteredione, insulin, and IGF-I, has been associated with obesity (51). Chlebowski showed analysis of participants in the Women's Health Initiative regarding the effects of energy intake and physical activity, suggesting that both physical activity and less food intake can reduce estrogen upregulates the IGF-I receptor and IGFBP-1 or -2. Chlebowski showed analysis of participants in the Women's Health Initiative regarding the effects of energy intake and physical activity, suggesting that both physical activity and less food intake can reduce energy intake and physical activity, suggesting that both physical activity and less food intake can reduce estrogen upregulates the IGF-I receptor and IGFBP-1 or -2. Estradiol, adiponectin, IGF-I or -II, or IGFBP-1 or -2.

Insulin resistance with compensatory hyperinsulinemia may, then, react with the overexpressed insulin and IGF receptors in breast cancer cells, leading to adverse outcome, suggesting that novel treatment strategies, including weight loss, physical activity, and pharmacologic intervention, may be appropriate. Goodwin mentioned that a number of trials of metformin treatment are planned.

Colorectal cancer. Jing Ma (Boston, MA) discussed the associations between insulin and risk of colorectal cancer, noting the “remarkable similarity” of the risk factors for type 2 diabetes and colon cancer. There are >50 studies suggesting an inverse association between physical activity and colon cancer (60), with a 30–50% risk reduction related to high activity. More than 20 studies support an inverse association between BMI and colon cancer, with a 1.3- to 2-fold increased risk associated with BMI >30 kg/m² that is consistently stronger in men than in women (perhaps because of the protective effect of estrogen) (61). A number of studies have been carried out suggesting that type 2 diabetes is associated with a 1.5-fold increased risk of colon cancer. The risk of colon cancer is greatest in per-
sons with type 2 diabetes at 11–15 years after diagnosis, suggesting a role of long-standing hyperinsulinemia (62).

References