Cancer Causes and Control **15**: 267–275, 2004.

Hyperinsulinaemia and increased risk of breast cancer: findings from the British women's heart and health study

Debbie A. Lawlor*, George Davey Smith & Shah Ebrahim
Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, UK

Received 15 August 2003; accepted in revised form 23 December 2003

Key words: aetiology, breast cancer, diabetes, hyperinsulinaemia, insulin resistance.

Abstract

Objective: To assess the association between fasting insulin levels and breast cancer.
Design: Cross sectional study.
Participants: 3868 women aged 60–79 years.
Main outcome measure: Prevalent breast cancer (151 cases).
Results: Insulin levels were positively associated with breast cancer. The age adjusted odds ratio (95% confidence interval) for a one unit increase in log(e) insulin levels among women without diabetes was 1.34 (1.02, 1.77). This association was not substantively altered by adjustment for potential confounding factors (age of menopause, hysterectomy/oophorectomy, hormone replacement use, oral contraceptive use, parity, adult social class and smoking) or potential mediating factors (body mass index, waist to hip ratio, leg length, age at menarche and childhood social class). Women with both long legs and higher insulin levels were at particularly increased risk, with breast cancer prevalence being 5.7% among women in the highest thirds of both insulin levels and leg-length compared to 1.8% among those in the lowest thirds of both. Positive associations between insulin levels and breast cancer were found for both pre- and post-menopausal breast cancers. Fasting glucose levels, HOMA score, diabetes and a history of gestational glycosuria or diabetes were also positively associated with breast cancer.
Conclusions: Hyperinsulinaemia is positively associated with breast cancer in this cohort of older women. This effect may be mediated *via* a number of hormonal pathways acting at different stages of the life course.

Introduction

It has been hypothesised that hyperinsulinaemia is associated with breast cancer risk and that this association may explain the relationship between western lifestyles and increased breast cancer occurrence [1–4]. Several mechanisms may link hyperinsulinaemia to breast cancer. First, chronic hyperinsulinaemia results in increased production of ovarian testosterone and oestrogen and inhibition of hepatic production of sex hormone binding globulin, a sex-hormonal profile that is associated with breast cancer [3, 5]. Second, hyperinsulinaemia suppresses hepatic production of insulin like growth factor binding protein-1 (IGFBP-1), and thus increases circulating levels of insulin like growth factor-1 (IGF-1). IGF-1 has a potent mitogenic effect on breast tissue [6] and plasma levels of IGF-1 in adulthood have in some [7–10], though not all [11, 12], epidemiological studies been found to be associated with breast cancer risk. Lastly, insulin itself may have a direct mitogenic effect, either *via* its affinity for IGF-1 receptors, or by a direct effect on DNA proliferation [4].

Whilst a number of small case control studies have found type 2 diabetes and other indicators of insulin resistance to be associated with breast cancer risk [13–15], fewer studies have directly assessed the association between insulin levels and breast cancer. This is important since the proposed mechanisms for the association are related directly to elevated levels of insulin. Three case control studies have found either C-peptide, a peripheral marker of insulin secretion, or insulin levels

* Address correspondence to: Dr D.A. Lawlor, Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, UK. Ph.: +44-117-928-7267; Fax: +44-117-928-7236/7292; E-mail: d.a.lawlor@bristol.ac.uk

to be positively associated with breast cancer independently of waist–hip ratio, body mass index and other potential confounding or mediating factors [1, 8, 16]. However, a recent prospective analysis of participants in the Atherosclerosis Risk in the Community (ARIC) study found that fasting insulin was not associated with breast cancer [17]. The participants in that study were relatively young (45–64 years), and although the authors did not report how many cases were pre-menopausal, it is likely that a large proportion were. It is possible that associations are stronger with post-menopausal cancers, which have been found more consistently than pre-menopausal cases to be associated with obesity [4, 18, 19].

From a health care perspective not only is it important to establish whether hyperinsulinaemia is associated with breast cancer, it is also important to establish the pathways that link insulin to breast cancer [19]. For example, insulin resistance and the associated hyperinsulinaemia may explain the association between post-menopausal obesity and breast cancer risk [4, 18], in which case interventions aimed at reducing obesity in adulthood would be important in breast cancer prevention. Alternatively, it has been suggested that pre-pubertal factors, which influence insulin resistance around the time of adolescence explain the association with breast cancer, and that prevention should be targeted towards childhood diet and levels of physical activity [3]. In support of this latter hypothesis, we have previously shown that leg-length (a biomarker of pre-pubertal environmental factors, such as diet, that affect linear growth [20]) is weakly positively associated with breast cancer [21]. Leg length is, however, inversely associated with insulin resistance in women and men [22, 23].

The aim of this study is to assess the association between fasting insulin levels and breast cancer, and to determine whether this association is explained by or interacts with biomarkers of pre-pubertal exposures (leg-length, age at menarche and childhood social class) or adult exposures (body mass index and waist to hip ratio).

Methods

Participants

The British Women's Heart and Health Study comprises 4286 (60% of those invited to participate) women aged 60–79 years randomly selected from general practitioner lists of 23 British towns [21, 22]. Ethics committee approvals were obtained for the study and written consent to access medical records and to flag the women with the National Health Service Cancer Register (NHSCR) were obtained from the participants. Participants completed a questionnaire and attended a local health centre where a research nurse interview, physical examination and blood sampling were undertaken. General practitioner (primary care) medical records (including computer and written records of primary care consultations, secondary care referral and discharge letters and correspondence between outpatient clinics and primary care) were reviewed for each participant and details of diagnoses of cardiovascular disease, diabetes and cancers extracted. Data were collected between April 1999 and March 2001 and full details of methods have been previously reported [21, 22].

Measurements

Three sources of data were used to determine breast cancer status: (i) women were asked if they had ever been told by a doctor that they had breast cancer and if so the date of diagnosis; (ii) diagnoses of breast cancer together with dates were extracted from the general practitioner medical records (including written records, computer records and hospital correspondence); and (iii) all participants were flagged with the National Health Service central register (NHSCR) which provided details of cancer registrations. Anyone with a diagnosis of breast cancer from any one of these three sources was considered to be a prevalent case. Flagging of participants with the NHSCR was continuous, and is still ongoing, from the time of the baseline fieldwork (completed in March 2001). We included all cases from the NHSCR that were reported to us by the NHSCR up to May 2003 (the time of the current analyses) and that had been diagnosed prior to the date that the woman attended for baseline study examination and blood sampling. Thus, this study is of prevalent breast cancer cases all of which had been diagnosed prior to blood sampling. The median time interval between diagnosis of breast cancer and blood sampling for participants with breast cancer in this study was 6 years with a range of 0.5–36 years; 25% of those with breast cancer had been diagnosed within 1 year of having the blood sampling. Cases were defined as pre- and post-menopausal based on self-report of age at menopause and the date of first diagnosis of breast cancer obtained from the GP record, cancer register or, if not available from these two sources, self-report ($n = 11$). For women who had had an oophorectomy prior to their natural menopause the date of the oophorectomy was taken as their date of menopause. For women who had had a hysterectomy without oophorectomy prior to their natural menopause

their age of menopause was assumed to be the median of the cohort – 50 years (n = 11 breast cancer cases), and for women with breast cancer who did not provide details of their age at menopause their age at menopause was assigned 50 years (n = 3).

Blood samples, for the whole cohort, were taken at the baseline examination after a minimum 6 h fast using evacuated tubes. Serum insulin was measured using an ELISA assay which does not cross react with proinsulin [24]. Fasting glucose was also measured and HOMA scores (a measure of insulin resistance) calculated as the product of fasting glucose (mmol/l) and insulin (μU/ml) divided by the constant 22.5. Diabetes was defined as anyone with a primary care medical record of a diagnosis of diabetes or treatment with oral hypoglycaemics or insulin and/or anyone with a self-report of a doctor diagnosis of diabetes (97% of cases were identified from both primary care records and self-report).

Standing height was measured without shoes using a Harpenden Stadiometer which recorded to the nearest millimetre. Weight was measured in light clothing without shoes to the nearest 0.1 kg using Soenhle portable scales. Body mass index was calculated as the weight in kilograms divided by height in meters squared. Waist measurements were taken using the mid-point between the lowest rib and iliac crest and hip measurements using the largest circumference below the waist. A flexible metal tape was used and two measurements taken to the nearest millimetre.

Age at menopause, age at menarche, parity, sex and birth weight of offspring, diagnoses of diabetes and glycosuria during pregnancy, current and past use of hormone replacement therapy and past use of oral contraception, history of a hysterectomy and/or oophorectomy, and smoking history were obtained from the self completed questionnaire and/or the research nurse interview [21, 22, 25]. All participants were requested to bring their medications to the research nurse interview and a full drugs history was taken. Adult social class was defined on the basis of the longest held occupation of her husband for married women and her own longest held occupation for single women, childhood social class was defined on the basis of the longest held occupation of the participants father, and both were classified according to the Registrar General's classification [26].

Statistical analysis

Means and prevalences of insulin, diabetes and other characteristics are presented for women with breast cancer and those without breast cancer and Student's t test and χ^2 statistics were used to assess differences in the distributions of these characteristics between women with and without breast cancer. Multiple logistic regression was used to assess the associations of insulin, glucose, HOMA scores, diabetes, self-report of gestational glycosuria or diabetes and having an offspring who was macrosomic (birth weight $\geq$ 4500 g) with breast cancer, with adjustment for potential confounding (age, use of oral contraception, use of hormone replacement, age at menopause, parity) or mediating variables (body mass index, waist to hip ratio, leg length, age at menarche, childhood social class). In these models age, age at menarche, age at menopause, body mass index and waist to hip ratio were entered as continuous variables. Hysterectomy and/or oophorectomy (yes, no), use of hormone replacement therapy (current, past, never), every use of oral contraception (yes, no), parity (0, 1, 2, 3, 4, $\geq$5), adult and childhood social class (I, II, III non-manual, III manual, IV, V) and smoking (never, ex and current) were entered as dummy variables so that no assumptions concerning linearity were made. Of the 4286 women 425 could not be assigned an adult social class and 545 could not be assigned to a childhood social class because they did not provide data on occupation. Although the participants were not specifically asked about unemployment these women are likely to have been married to unemployed men (for those with missing adult data) and had fathers who were unemployed (for those with missing childhood data). This is consistent with the findings that women without these data on social class were more likely to smoke, more likely to be obese, were shorter and were more likely to have prevalent coronary heart disease than cohort members who provided these data [27]. In the main analysis women with missing social class data were allocated to social class V, the most deprived group. A sensitivity analysis was conducted in which these women were excluded from the analysis. These results did not differ substantively from the main analyses and have not been presented in this paper. To determine whether there was an interaction between insulin and leg length (*i.e.*, whether for example women with longer legs, indicative of greater linear growth and possibly greater exposure to IGF-1 in childhood, and also greater insulin exposure in adulthood were at particularly increased risk of breast cancer), both variables were categorised into thirds and the prevalence of breast cancer across these thirds were assessed. A likelihood ratio test was used to assess statistical evidence for an interaction. Insulin and glucose levels and HOMA scores were positively skewed but were log normal; geometric means are presented and the natural logarithms of the values were used in all regression models. In all analyses robust standard errors, taking into account possible non-independence between

women from the same town, were used to estimate confidence intervals. All analyses were conducted using Stata version 8.0 (Stata corporation, Texas 2002).

Results

The prevalence of breast cancer among women who were invited to take part in the study but did not respond was obtained from GP record reviews in 21 of the 23 practices – the proportion of general practice recorded breast cancer did not differ between responders and non-responders (3.1% (95% confidence interval 2.6, 3.7%) *versus* 2.8% (2.2, 3.5%), $p = 0.7$). Of the 4286 women 3868 (90%) had adequate fasting blood samples for insulin and glucose assessment; all subsequent analyses are undertaken on these 3868 women only. There were no differences in age, breast cancer, body mass index, waist to hip ratio, systolic blood pressure or social class distributions between those with these data and those who did not have these data (all p values >0.2). Of these 3868 women, 151 had breast cancer ascertained from at least one source, giving an overall prevalence of 3.9% (95% confidence interval 3.3–4.6%). The majority (89%) of these cases were identified from at least two sources. The age distribution of women with cancer identified by each source were similar – mean (standard deviation) age of women with breast cancer identified by self-report 68.5 (5.3), identified by medical record review 68.4 (5.3) and identified by cancer register 68.6 (5.3). Of the 151 cases 36 (23.8%) were pre-menopausal and 115 (76.2%) were post-menopausal. Of the 3868 women included in the analyses 203 (5.3%) had clinically diagnosed diabetes. For all analyses concerning fasting insulin, glucose and HOMA scores these women were excluded.

Table 1 shows mean fasting insulin, glucose, HOMA scores, diabetes prevalence and the distributions of other characteristics of the women by their breast cancer status. Women with breast cancer had higher fasting insulin and glucose levels and higher HOMA scores than those without breast cancer, and were more likely to have diabetes, or to have experienced gestational diabetes or glycosuria in pregnancy. Neither adult central (waist to hip ratio) nor general (body mass index) obesity were strongly associated with breast cancer status. Age at menarche was not associated with breast cancer status, but women with breast cancer had an older age of menopause, were less likely to have had a hysterectomy and/or oophorectomy, were more likely to have ever used hormone replacement and were more likely to be nulliparous. Ever use of oral contraception

Table 1. Characteristics of women, aged 60–79 years, with and without breast cancer

	Women with breast cancer (n = 147)	Women without breast cancer (n = 3690)	*p*
Continuous variables: *means* (*SD*)			
Age (years)	68.5 (5.3)	68.9 (5.5)	0.4
Fasting insulin (μU/ml)[a]	1.90 (1.80, 2.00)	1.77 (1.76, 1.79)	0.03
Fasting glucose (mmol/l)[a]	6.09 (5.89, 6.29)	5.90 (5.87, 5.93)	0.07
HOMA score[a]	1.86 (1.67, 2.05)	1.65 (1.62, 1.70)	0.05
Age at menarche (years)	13.3 (1.9)	13.3 (1.7)	0.7
Age at menopause (years)	49.0 (5.4)	48.1 (5.9)	0.05
Body mass index (kg/m^2)	28.1 (5.6)	27.6 (5.0)	0.21
Waist to hip ratio (as a %)	81.92 (6.15)	81.89 (6.84)	0.9
Total height (mm)	1598.5 (53.3)	1585.9 (64.2)	0.02
Leg length (mm)	762.5 (37.3)	757.2 (41.3)	0.11
Dichotomous variables: *percentage* (*95% CI*)			
Diabetes	9.6 (5.7, 15.5)	6.7 (5.9, 7.6)	0.17
Gestational glycosuria or diabetes	4.9 (1.9, 9.3)	2.8 (2.3, 3.4)	0.23
Offspring with macrosomia	1.9 (0.5, 6.2)	1.4 (1.0, 1.8))	0.76
Nulliparity	14.3 (9.5, 20.9)	8.8 (7.9, 9.7)	0.02
Hysterectomy and/or oophorectomy	23.6 (27.2, 30.1)	28.6 (27.2, 30.1)	0.18
Ever use of HRT	21.0 (15.0, 28.6)	14.6 (13.4, 15.9)	0.04
Ever use of oral contraception	28.1 (21.2, 36.1)	23.9 (22.5, 25.3)	0.3
Adult manual social class	53.4 (45.0, 61.0)	56.4 (54.8, 58.0)	0.4
Childhood manual social class	77.6 (70.1, 83.6)	80.0 (78.6, 81.1)	0.5
Ever smoke	49.7 (42.2, 57.2)	50.7 (49.2, 52.2)	0.8

[a] Geometric means (95% confidence intervals). SD: standard deviation; CI: confidence interval; HRT: hormone replacement therapy.

Table 2. Association of fasting insulin with breast cancer, with adjustment for potential mediating and confounding factors, among women without diabetes

	Fully (age and variable in first column) adjusted odds ratio of breast cancer for an increase in a one unit log(e) insulin
Potential confounders included in fully adjusted model	
Age menopause	1.32 (0.99, 1.75)
Hysterectomy/oophorectomy	1.34 (1.01, 1.77)
HRT use	1.34 (1.01, 1.77)
Ever use oral contraception	1.36 (1.03, 1.81)
Parity	1.33 (1.01, 1.76)
Adult social class	1.35 (1.02, 1.78)
Cigarette smoking	1.34 (1.02, 1.77)
Potential mediators included in fully adjusted model	
Body mass index	1.32 (1.00, 1.80)
Waist to hip ratio	1.38 (1.02, 1.85)
Childhood social class	1.35 (1.02, 1.78)
Age menarche	1.36 (1.03, 1.81)
Leg length	1.37 (1.03, 1.81)
Total height	1.36 (1.03, 1.80)
All potential confounding and mediating variable	
Fully adjusted for age and all potential confounding and mediating factors as listed above	1.35 (1.00, 1.81)

was also slightly greater among women with breast cancer. Neither childhood nor adult social class were strongly associated with breast cancer status, but there was a tendency for women with breast cancer to have longer legs and to be taller. Smoking status was not strongly associated with breast cancer status.

Table 2 shows the associations between fasting insulin and breast cancer with adjustment for potential confounding and mediating variables. This table contains results for women without diabetes (n = 3665). Since there were some missing data for some of the potential confounding or mediating variables the age adjusted odds ratio for only those women with complete data on the particular variable that is being included in the fully adjusted model was assessed. In this way one can be clear that any effect of adjustment is not due to analyses being performed on a sub-group of those included in the age adjusted model. The distribution of breast cancer did not differ between those with complete data and those with missing data for any of the variables. Among all of the women without diabetes the age adjusted odds ratio for a one unit increase in log(e) insulin was 1.34 (95% confidence interval, 1.02, 1.77). None of the age adjusted associations in each sub-group with complete data on the variable(s) adjusted for differed from this age adjusted estimate for all participants: point estimates were all between 1.32 and 1.37. The positive age-adjusted association between fasting insulin and breast cancer was not substantively altered by adjustment for any of the other potential confounding or mediating variables. Among the sub-group with complete data on all potential confounding and mediating factors (n = 2985) the age adjusted odds ratio for an increase of one unit of log(e) insulin level was 1.32 (0.98, 1.76), with adjustment for all potential confounding and mediating variables this increased slightly to 1.35 (1.00, 1.81). An increase of one log(e) unit of insulin is a large increase; the age adjusted odds ratio for an increase of one quarter of the distribution of fasting insulin (i.e. going from the lowest quarter to the second, or second to the third, or third to highest quarter) among all women without diabetes (n = 3665) was 1.17 (1.01, 1.36).

Breast cancer prevalence was greatest among women who had both high insulin levels and who had longer legs, being 5.7% among those in the highest thirds of both insulin level and leg-length compared to 1.8% among those in the lowest thirds of both (Figure 1). In logistic regression models fasting insulin and leg-length combined multiplicatively, with a model including both of these explanatory variables being a better fit of the breast cancer outcome than models including just one of them. There was no evidence to suggest a statistical interaction ($p = 0.6$) – that is insulin and leglength did not appear to combine with a greater than multiplicative effect.

Of the 151 women with prevalent breast cancer 49 were taking tamoxifen at the time of their examination and blood testing. When these 49 were excluded from the analysis the association between fasting insulin levels

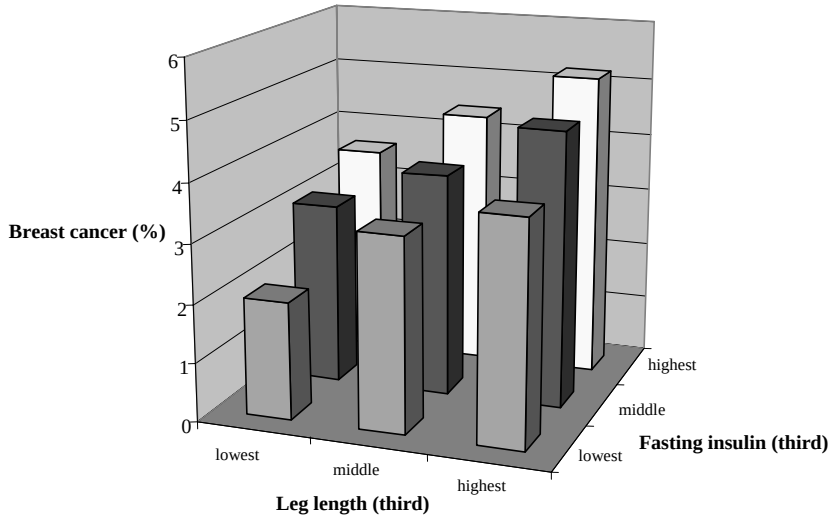

Fig. 1. Prevalence (%) of breast cancer by fasting insulin level and leg length.

and breast cancer was essentially unchanged: 1.37 (0.95, 1.95). When associations with post-menopausal and pre-menopausal cancers were estimated separately the positive association of fasting insulin was found for both cancer types, although the reduced numbers of cases in these analyses make the results imprecise. The age adjusted odds ratio for an increase of one unit of log insulin was 1.24 (0.71, 2.19) comparing pre-menopausal cancers to having no cancer (n = 36) and 1.36 (0.99, 1.89) comparing post-menopausal cancer to no cancer (n = 115), p for difference between these = 0.14.

There was a linear association across quarters of fasting insulin and women with diabetes (Figure 2). Among all women the age adjusted association between diabetes and breast cancer was 1.50 (0.85, 2.65). As with insulin breast cancer prevalence was greatest among those who were diabetic and in the highest third for leg length (9.9%) compared to those who were non-diabetic and in the lowest third for leg length (3.0%). The association between diabetes and breast cancer was attenuated to 1.42 (0.82, 2.59) with adjustment for body mass index, but was not substantively affected by adjustment for any other potential confounding or mediating factor. The age adjusted odds ratio for a one unit increase in log(e) HOMA score was 1.31 (0.99, 1.74), with adjustment for all potential confounding and mediating factors this attenuated to 1.28 (0.96, 1.72). Of the 3301 women who had at least one offspring 123 (3.7%) reported having either glycosuria during a pregnancy or being diagnosed with gestational diabetes (n = 8). Among women with at least one offspring, having either gestational glycosuria or diabetes was associated with increased odds of breast cancer: age adjusted odds ratio 1.59 (0.72, 3.49). Only 45 (1.4%) of women with at least one offspring had a baby of birth weight 4500 g or more; these women had a slightly increased odds of breast cancer 1.18 (0.65, 2.17).

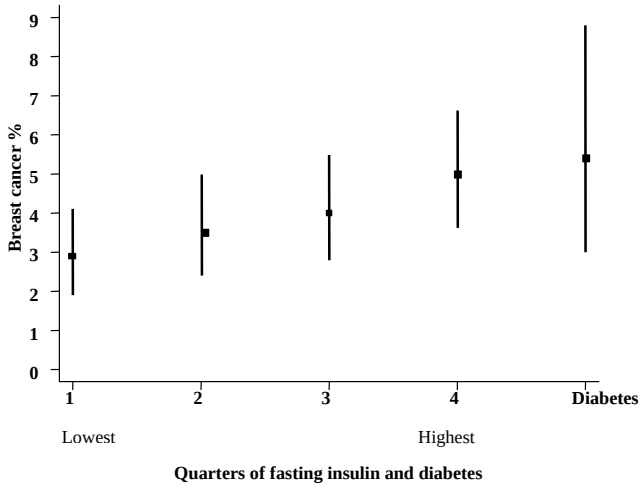

Fig. 2. Prevalence of breast cancer (95% confidence interval) by quarters of fasting insulin/diabetes.

When all analyses were repeated using breast cancer data from each of just one of the three sources (cancer register, general practice medical records, self-report) the results were unchanged.

Discussion

We have found a positive association between high fasting insulin and breast cancer. In addition, although some estimates were imprecise, fasting glucose, HOMA

score, diabetes and gestational glycosuria or diabetes were also positively associated with breast cancer risk, suggesting that previous exposure to high circulating insulin levels, as well as contemporary exposure, is related to increased risk of breast cancer. There was a positive linear association across the distribution of fasting insulin and diabetes with breast cancer (Figure 2). These associations were not explained by potential confounding or mediating factors, but women with both longer legs and greater insulin levels were at particularly high risk of having breast cancer. Leg length is a useful biomarker of pre-pubertal exposures that affect linear growth and may reflect levels of IGF-1 in early life [19].

Study limitations

Our response rate (60%) is moderate but the prevalences of general practitioner recorded cases of breast cancer were similar between responders and non-responders in our study. Our study is cross sectional and survivor bias may be an important limitation. Breast cancer in the UK is associated with a survival rate of 70% over 5 years [28]. Our study may therefore exclude a number of women with the most aggressive form of breast cancer. This would have an important effect on the results if insulin resistance was associated with reduced mortality from breast cancer in which case our results, and those of a number of case–control studies, would be an exaggeration of the true association between insulin resistance and breast cancer. However, in one prospective study of women with early stage breast cancer insulin levels were found to be positively associated with distant recurrence and mortality [29], suggesting that survivor bias is unlikely to explain our results. Reverse causality may explain our results if women who were diagnosed with breast cancer became less active, more obese and as a result more insulin resistant. Adult obesity did not explain the association between insulin resistance and breast cancer and only partially explained the association between diabetes and breast cancer in our study. Breast cancer cases were not confirmed histologically and self-report of breast cancer may be inaccurate. However, 89% of the cases were identified from at least two sources, including medical records, cancer registers or self-report, with only 8 cases being identified solely from self-report and no other source. Medical record and cancer register cases are likely to have been confirmed by histological reports and when sensitivity analyses were performed using breast cancer data from each of just one of the three sources (cancer register, general practice medical records, self-report) the results were unchanged. By combining information from all three sources it is likely that most cases have been identified. Tamoxifen may affect liver enzymes and hypertriglyceridaemia has been reported with its use. It is possible therefore that the association between hyperinsulinaemia and breast cancer may reflect an association between tamoxifen and hyperinsulinaemia. However, we found a positive association even when the analyses were restricted to those women who were not taking tamoxifen at the time of having their insulin levels assessed. The associations between age at menopause, hysterectomy/oophorectomy, hormone replacement therapy use and nulliparty and breast cancer are similar to those reported in several prospective and case–control studies [30], providing support for our results not being fully explained by either survivor bias or reverse causality.

Insulin resistance, IGFs and sex hormones across the life course and breast cancer risk

Our results are consistent with most previous studies in this area [1, 8, 9, 16]. A case–control study nested within the Rancho–Bernardo cohort study found no association between either fasting insulin or C-peptide levels, but that study was small with only 45 cases and other established risk factors for breast cancer including parity, age at menopause, height and body mass index were not associated with breast cancer in that study [31]. One large prospective cohort study (ARIC) found no association between fasting insulin levels and breast cancer risk, though there was a positive association with fasting glucose [17]. Although most studies suggest a positive association, there are inconsistencies and additional large prospective studies are required to confirm a positive association with a high level of certainty. Figure 3 represents the pathways through which hyperinsulinaemia and other hormonal factors across the life course may affect breast cancer risk [32]. Further more detailed studies with physiological, biochemical as well as behavioural exposures from across the life course are required to determine which of these pathways are relevant.

Leg-length appears to be the component of height that is most importantly influenced by pre-pubertal factors affecting linear growth, and is influenced by infant feeding and childhood diet [20, 33]. Both higher insulin levels and greater leg-length [21] are associated with increased breast cancer risk in the British Women's Heart and Health Study cohort. We found that the association between hyperinsulinaemia and breast cancer was independent of leg length, and that women who were in the highest distributions of both insulin levels and leg length were at particularly high risk of breast cancer, suggesting that these two risk factors may

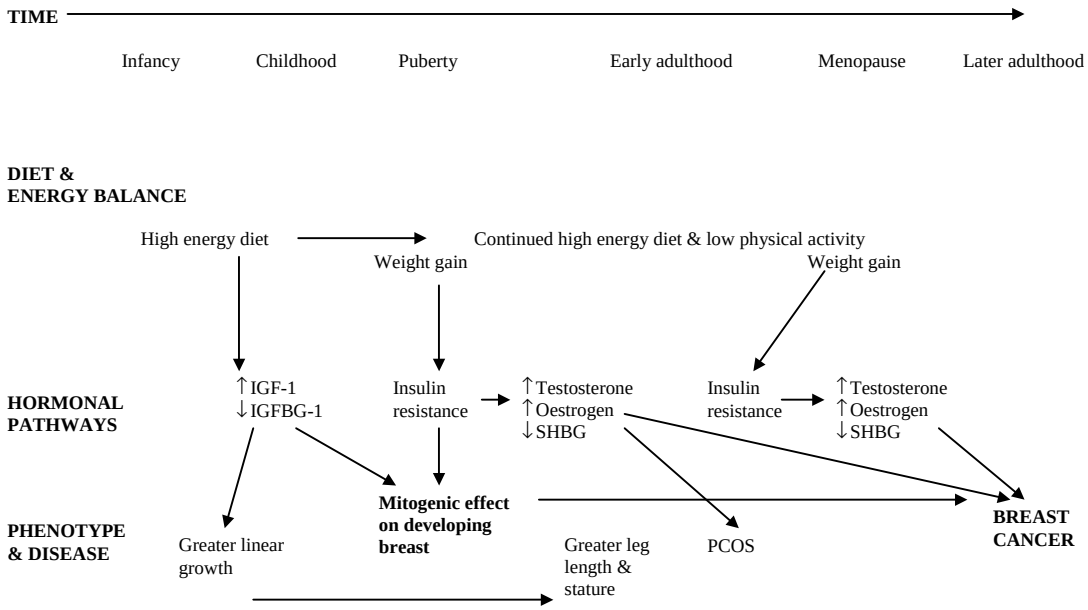

Fig. 3. Hypothesised pathways for the life course associations of insulin resistance and other hormonal axes with breast cancer: IGF: insulin like growth factor; IGFBG: insulin like growth factor binding globulin; SHBG: sex hormone binding globulin; PCOS: polycystic ovarian syndrome.

operate through different mechanisms. Greater leg-length may predominantly reflect higher circulating levels of IGF-1 during the pre-pubertal period, and around the time of puberty, whereas insulin levels may reflect life time exposure to high energy diets, and have an direct effect on breast cancer risk through an effect on sex hormones (as discussed above) or *via* a direct mitogenic effect (Figure 3).

Growth hormone affects cellular growth through the actions of IGFs. Serum IGF levels are also affected by diet [34]. In children IGF-I levels are positively associated with stature and during pubertal growth periods, IGF-I serum levels can be as high as four times the normal adult concentration [34]. In energy-restricted mice administration of IGF-I reverses their decreased cancer risk [12]. However, in epidemiological studies inconsistent findings have been reported for the association between adult plasma levels of IGF-I and breast cancer [7–12]. Studies of pubertal levels of IGF-1 levels and breast cancer have not been assessed and adult levels may not be an adequate indicator of earlier levels particularly during growth spurts.

Implications

Our findings, together with others, suggest that hyperinsulinaemia is associated with increased risk of breast cancer. This effect is likely to reflect cumulative and interacting effects with hormonal pathways involving IGFs and sex hormones across the life course (Figure 3). If our hypotheses are correct then they suggest that interventions in childhood and later life aimed at preventing insulin resistance (low energy diets and increased levels of physical activity) are important for preventing breast cancer. Recent increases in childhood obesity, particularly of central obesity in girls [35], may result in increases in breast cancer incidence. Future research should directly assess the influence of childhood diet and other early life exposures on breast cancer risk.

Acknowledgements

The British Women's Heart and Health Study is co-directed by Professor Shah Ebrahim, Professor Peter Whincup, Dr Goya Wannamethee and Dr Debbie A Lawlor. We thank Carol Bedford, Alison Emerton, Nicola Frecknall, Karen Jones, Rita Patel, Mark Taylor and Katherine Wornell for collecting and entering data, all of the general practitioners and their staff who have supported data collection and the women who have participated in the study.

Contributions: All authors developed the study aim and design. DAL undertook the initial analysis and coordinated writing of the paper. All authors contributed to the final version. DAL acts as guarantor.

Funding: The British Women's Heart and Health Study is funded by the Department of Health. DAL was funded by a Medical Research Council/Department of

Health (UK) Training Fellowship when this work was conducted and is now funded by a Department of Health (UK) Career Scientist Award. The views expressed in this publication are those of the authors and not necessarily those of any of the funding bodies.

Conflict of interests: None.

References

1. Bruning PF, Bonfrer JM, van Noord PA, Hart AA, Jong-Bakker M, Nooijen WJ (1992) Insulin resistance and breast-cancer risk. *Int J Cancer* **52**: 511–516.
2. Kazer RR (1995) Insulin resistance, insulin-like growth factor I and breast cancer: a hypothesis. *Int J Cancer* **62**: 403–406.
3. Kaaks R (1996) Nutrition, hormones, and breast cancer: is insulin the missing link? *Cancer Causes Control* **7**: 605–625.
4. Stoll BA (2002) Upper abdominal obesity, insulin resistance and breast cancer risk. *Int J Obes Relat Metab Disord* **26**: 747–753.
5. Berrino F, Bellati C, Secreto G, *et al*. (2001) Reducing bioavailable sex hormones through a comprehensive change in diet: the diet and androgens (DIANA) randomized trial. *Cancer Epidemiol Biomarkers Prev* **10**: 25–33.
6. Druckmann R, Rohr UD (2002) IGF-1 in gynaecology and obstetrics: update 2002. *Maturitas* **41(**Suppl 1): S65–S83.
7. Hankinson SE, Willett WC, Colditz GA, *et al*. (1998) Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet* **351**: 1393–1396.
8. Del Giudice ME, Fantus IG, Ezzat S, McKeown-Eyssen G, Page D, Goodwin PJ (1998) Insulin and related factors in premenopausal breast cancer risk. *Breast Cancer Res Treat* **47**: 111–120.
9. Toniolo P, Bruning PF, Akhmedkhanov A, *et al*. (2000) Serum insulin-like growth factor-I and breast cancer. *Int J Cancer* **88**: 828–832.
10. Krajcik RA, Borofsky ND, Massardo S, Orentreich N (2002) Insulin-like growth factor I (IGF-I), IGF-binding proteins, and breast cancer. *Cancer Epidemiol Biomarkers Prev* **11**: 1566–1573.
11. Kaaks R, Lundin E, Rinaldi S, *et al*. (2002) Prospective study of IGF-I, IGF-binding proteins, and breast cancer risk, in northern and southern Sweden. *Cancer Causes Control* **13**: 307–316.
12. Petridou E, Papadiamantis Y, Markopoulos C, Spanos E, Dessypris N, Trichopoulos D (2000) Leptin and insulin growth factor I in relation to breast cancer (Greece). *Cancer Causes Control* **11**: 383–388.
13. Glicksman AS, Myers WPL, Rawson RW (1956) Diabetes mellitus and carbohydrate metabolism in patients with cancer. *Med Clin North Am* **40**: 887–900.
14. Muck BR, Trotnow S, Hommel G (1975) Cancer of the breast, diabetes and pathological glucose tolerance. *Arch Gynakol* **220**: 73–81.
15. Sinagra D, Amato C, Scarpilta AM, *et al*. (2002) Metabolic syndrome and breast cancer risk. *Eur Rev Med Pharmacol Sci* **6**: 55–59.
16. Yang G, Lu G, Jin F, *et al*. (2001) Population-based, case–control study of blood C-peptide level and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* **10**: 1207–1211.
17. Mink PJ, Shahar E, Rosamond WD, Alberg AJ, Folsom AR (2002) Serum insulin and glucose levels and breast cancer incidence: the atherosclerosis risk in communities study. *Am J Epidemiol* **156**: 349–352.
18. Lovegrove JA (2002) Obesity, body fat distribution and breast cancer. *Nutr Res Rev* **15**: 389–412.
19. Okasha M, McCarron P, Gunnell D, Davey Smith G (2003) Exposures in childhood, adolescence and early adulthood and breast cancer risk: a systematic review of the literature. *Breast Cancer Res Treat* **78**: 223–276.
20. Gunnell D (2002) Commentary: can adult anthropometry be used as a 'biomarker' for prenatal and childhood exposures? *Int J Epidemiol* **31**: 390–394.
21. Lawlor DA, Okasha M, Gunnell D, Davey Smith G, Ebrahim S (in press) The associations of adult measures of childhood growth with breast cancer: findings from the British Women's Heart and Health Study. *Br J Cancer*.
22. Lawlor DA, Ebrahim S, Davey Smith G (2002) The association between components of adult height and type II diabetes and insulin resistance: British Women's Heart and Health Study. *Diabetologia* **45**: 1097–1106.
23. Davey Smith G, Greenwood R, Gunnell D, Sweetnam P, Yarnell J, Elwood P (2001) Leg length, insulin resistance, and coronary heart disease risk: the Caerphilly Study. *J Epidemiol Commun Health* **55**: 867–872.
24. Andersen L, Dinesen B, Jorgensen PN, Poulsen F, Roder ME (1993) Enzyme immunoassay for intact human insulin in serum or plasma. *Clin Chem* **39**: 578–582.
25. Lawlor DA, Davey Smith G, Ebrahim S (2002) Birth weight of offspring and insulin resistance in late adulthood: cross sectional survey. *BMJ* **325**: 359.
26. Office of Population Censuses and Surveys (1980) *Classification of Occupations and Coding Index*. London: HM Stationary Office.
27. Lawlor DA, Ebrahim S, Davey Smith G (2002) Socioeconomic position in childhood and adulthood and insulin resistance: cross sectional survey using data from the British Women's Heart and Health study. *BMJ* **325**: 805–807.
28. Coleman MP, Babb P, Damecki P, Groscalude P, Hanjos S, Jones J (1999) *Cancer Survival Trends in England and Wales 1971–1995: Deprivation and NHS Region*. London: stationary Office.
29. Goodwin PJ, Ennis M, Pritchard KI, *et al*. (2002) Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol* **20**: 42–51.
30. dos Santos Silva I, De Stavola BL (2002) Breast cancer aetiology: where do we go from here? In: Kuh D, Hardy R, eds. *A Life Course Approach to Women's Health*. Oxford: OUP, pp.45–63.
31. Jernstrom H, Barrett-Connor E (1999) Obesity, weight change, fasting insulin, proinsulin, C-peptide, and insulin-like growth factor-1 levels in women with and without breast cancer: the Rancho Bernardo Study. *J Women's Health Gender-Based Med* **8**: 1265–1272.
32. Okasha M, McCarron P, Gunnell D, Davey Smith G (2003) Exposures in childhood, adolescence and early adulthood and breast cancer risk: a systematic review of the literature. *Breast Cancer Res* **78**: 223–276.
33. Wadsworth MEJ, Hardy RJ, Paul AA, Marshall SF, Cole TJ (2002) Leg and trunk length at 43 years in relation to childhood health, diet and family circumstances; evidence from the 1946 national birth cohort. *Int J Epidemiol* **31**: 383–390.
34. Okasha M, Gunnell D, Holly J, Davey Smith G (2002) Childhood growth and adult cancer. *Best Pract Res Clin Endocrinol Metab* **16**: 225–241.
35. McCarthy HD, Ellis SM, Cole TJ. (2003) Central overweight and obesity in British youth aged 11–16 years: cross sectional surveys of waist circumference. *BMJ* **326**: 624.