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British Journal of Cancer, 93(7)

0007-0920

Willett, E
Skibola, C
Adamson, P
et al.

2005-10-03

10.1038/sj.bjc.6602762

Peer reviewed
Non-Hodgkin’s lymphoma, obesity and energy homeostasis polymorphisms

EV Willett*,1,4, CF Skibola2,4, P Adamson1, DR Skibola2, GJ Morgan3, MT Smith2 and E Roman1

1Epidemiology and Genetics Unit, Department of Health Sciences, Seabourn Rowntree Building, University of York, York Y01 5DD, UK; 2Division of Environmental Health Sciences, School of Public Health, 140 Earl Warren Hall, University of California, Berkeley, CA 94720-7360, USA; 3Institute of Cancer Research, The Royal Marsden, Downs Road, Sutton, Surrey SM2 5PT, UK

A population-based case–control study of lymphomas in England collected height and weight details from 699 non-Hodgkin’s lymphoma (NHL) cases and 914 controls. Obesity, defined as a body mass index (BMI) over 30 kg m−2 at five years before diagnosis, was associated with an increased risk of NHL (OR = 1.5, 95% CI 1.1–2.1). The excess was most pronounced for diffuse large B-cell lymphoma (OR = 1.9, 95% CI 1.3–2.8). Genetic variants in the leptin (LEP 19G > A, LEP –2548G > A) and leptin receptor genes (LEPR 223Q > R), previously shown to modulate NHL risk, as well as a polymorphism in the energy regulatory gene adiponectin (APM1 276G > T), were investigated. Findings varied with leptin genotype, the risks being decreased with LEP 19AA (OR = 0.7, 95% CI 0.5–1.0) and increased with LEP –2548GA (OR = 1.3, 95% CI 1.0–1.7) and –2548AA (OR = 1.4, 95% CI 1.0–1.9), particularly for follicular lymphoma. These genetic findings, which were independent of BMI, were stronger for men than women.

British Journal of Cancer (2005) 93, 811 – 816. doi:10.1038/sj.bjc.6602762 www.bjcancer.com
Published online 13 September 2005
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Keywords: non-Hodgkin’s lymphoma; body mass index; SNP; leptin; adiponectin; epidemiology

MATERIALS AND METHODS

Details of this case–control study are described elsewhere (Willett et al, 2004). Briefly, cases were patients aged 18–64 years newly diagnosed with lymphoma between January 1998 and March 2001. Diagnoses were pathologically confirmed and coded to the World Health Organisation Classification (Fritz et al, 2000), and patients were ineligible if they had a previous diagnosis of lymphoma or HIV. One control per case, individually matched on sex and date of birth, was randomly selected from population registers. All participants were interviewed in person, and asked to provide a blood sample for research purposes. Study subjects were assigned an area-based indicator of deprivation by coding the enumeration districts (ED) where subjects resided at diagnosis/reference date to categories of the 1991 census-derived Townsend scores of EDs across England and Wales (Townsend et al, 1988). The study was conducted with the ethical approval of the United Kingdom Multi-Regional Ethical Committee.

At interview, participants were asked what their height and weight was at 5, 10 and 20 years prior to diagnosis/reference date. Body mass index was computed by dividing weight in kilograms by the square of height in metres. Height was categorised based on the observed distributions among controls who were aged 18 years or over at each time point. Body mass index was grouped into underweight (< 18.5 kg m−2), normal (18.5–24.99 kg m−2), grade 1 overweight (25–29.99 kg m−2), and grades 2 and 3 overweight (≥ 30 kg m−2).
DNA was isolated from peripheral blood mononuclear cells using a modified phenol–chloroform extraction and was quantified using Picogreen® dsDNA Quantitation kits (Molecular Probes, Eugene, OR, USA), according to the manufacturer’s specifications. Samples, blinded to case–control status, were genotyped using Taqman®-based assays designed by Applied Biosystems (ABI) (Applied Biosystems, Foster City, CA, USA). Reactions were performed on an ABI 7700 or GeneAmp PCR 9700 System for 10 min at 95°C, then 40 cycles of 95°C for 15 s and 60°C for 1 min; a post-PCR plate read on the ABI 7700 system was used to determine genotype. Genotyping probes and primers used are listed in Table 1. To ensure reproducibility of the genotyping procedure, replicate quality control samples were included with an agreement rate of over 99%.

Interviews were conducted with 912 lymphoma patients and 919 controls, 75% of cases and 71% of the controls identified, and blood samples were received from 843 (94%) cases and 829 (95%) controls who were interviewed. Among the 820 Caucasian cases and 826 Caucasian controls who gave a blood sample, 736 (90%) controls who were interviewed. Among interviewed cases with a confirmed diagnosis, 317 (45%) were interviewed (OR = 0.9, 95% CI 0.3–1.0, P = 0.06; >1.73 m: OR = 0.4, 95% CI 0.2–1.0, P = 0.06).

Using the WHO categorisation of BMI (Table 3), risks were estimated relative to cases and controls who were of normal weight-for-height. Persons who were underweight were at increased risk of NHL and DLBCL but not for FL; a 5 kg m⁻² rise in BMI increasing the risk of DLBCL by 30% (95% CI 1.2–1.5, P < 0.0001). These patterns were similar for men and women (data not shown). With respect to age at diagnosis, there was some suggestion that the risk of NHL associated with being markedly overweight may be more pronounced at younger ages: the OR falling from 2.7 (95% CI 1.2–5.8, P = 0.01), to 1.8 (95% CI 1.0–3.3, P = 0.04) to 1.2 (95% CI 0.8–1.9, P = 0.42) in those aged under 45, 45–54 and 55 years or more, respectively. Further, among the under 45 s, the finding was stronger for DLBCL (OR = 3.0, 95% CI 1.2–7.5, P = 0.02) than for FL (OR = 1.8, 95% CI 0.5–6.3, P = 0.33). Within the DLBCL subtype, risks were greater among men aged less than 45 (OR = 4.7, 95% CI 1.1–19.4, P = 0.03 based on five cases and four controls) than among women of the same age group (OR = 2.5, 95% CI 0.7–8.6, P = 0.15 based on five cases and 10 controls). Analyses were repeated using anthropometric data at 10 and 20 years before diagnosis/reference date, and using the individually
matched controls alone and conditional logistic regression, and the findings were similar (data not shown).

Genotype distributions for cases and controls for the LEP 19G>A, LEP –2548G>A, LEPR 223Q>R and APM1 276G>T polymorphisms are shown in Table 4. Control genotype distributions for all SNPs were in Hardy–Weinberg equilibrium. Relative to LEP 19GG, the LEP 19AA genotype was inversely associated with FL (OR = 0.5, 95% CI 0.3 – 0.8, P = 0.01), but not DLBCL (OR = 0.9, 95% CI 0.6 – 1.4, P = 0.70). For LEP –2548G>A, an increased risk for NHL was observed among carriers of the LEP –2548GA (OR = 1.3, 95% CI 1.0 – 1.7, P = 0.03) and LEP –2548AA genotypes (OR = 1.4, 95% CI 1.0 – 1.9, P = 0.04), particularly for FL (LEP –2548GA: OR = 1.6, 95% CI 1.1 – 2.3, P = 0.01; LEP –2548AA: OR = 1.4, 95% CI 0.9 – 2.3, P = 0.12) when compared to LEP –2548GG carriers. Stratifying by sex revealed that among men, the LEP 19AA genotype was associated with a reduced risk of NHL (OR = 0.6, 95% CI 0.4 – 1.0, P = 0.06) and FL (OR = 0.3, 95% CI 0.1 – 0.7, P = 0.005), while the LEP –2548AA genotype was associated with an increased risk of NHL (OR = 1.6, 95% CI 1.1 – 2.5, P = 0.02), DLBCL (OR = 1.6, 95% CI 1.0 – 2.7, P = 0.07) and FL (OR = 1.8, 95% CI 0.9 – 3.5, P = 0.10). No associations were found in women with the exception of an increased risk of FL among carriers of the LEP 223RR (OR = 1.9, 95% CI 1.0 – 3.6, P = 0.04) relative to the LEP 223QQ genotype. There were no differences in genotype distributions between cases and controls for the APM1 276G>T SNP. Tests for interactions between

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**Table 2** Number of cases and controls, adjusted odds ratios and 95% confidence intervals for height

| Heighta | Control Case ORc 95% CI | Case ORc 95% CI | Case ORc 95% CI |
|---------|----------------------|----------------|----------------|
| Males   |                      |                |                |
| ≤1.65   | 495 361              | 167            | 103            |
| 1.65–1.73 | 139 103            | 45             | 32             |
| 1.74–1.80 | 214 151            | 63             | 47             |
| 1.81–1.88 | 104 82             | 45             | 19             |
| >1.88   | 12 6                | 3              | 1              |
| Females |                      |                |                |
| ≤1.52   | 419 338              | 150            | 125            |
| 1.53–1.57 | 82 74             | 28             | 34             |
| 1.58–1.68 | 226 171           | 86             | 55             |
| 1.69–1.73 | 56 38              | 18             | 11             |
| >1.73   | 12 20               | 8              | 6              |

aBody mass index (BMI) at 5 years prior to diagnosis/reference date where BMI categorised as underweight: < 18.5 kg m\(^{-2}\); normal: 18.5 – 24.99 kg m\(^{-2}\); grade 1 overweight: 25 – 29.99 kg m\(^{-2}\); grades 2 and 3 overweight: ≥ 30 kg m\(^{-2}\) (WHO Expert Committee on Physical Status, 1995). BMI was missing for four cases and three controls as weight was not reported. bNHL = Non-Hodgkin’s lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma. Odds ratios adjusted for age and region estimated using unconditional logistic regression.

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**Table 3** Number of cases and controls, adjusted odds ratios and 95% confidence intervals by age for body mass index

| BMIa  | Control Case ORc 95% CI | Case ORc 95% CI | Case ORc 95% CI |
|-------|----------------------|----------------|----------------|
| Total |                      |                |                |
| Underweight | 14 5          | 2              | 0              |
| Normal      | 510 347       | 159            | 120            |
| Grade 1     | 298 247       | 99             | 80             |
| Grades 2 and 3 | 89 69       | 54             | 27             |
| <45 years   | 202 107       | 60             | 29             |
| Underweight | 4 1           | 1              | 0              |
| Normal      | 133 101       | 32             | 18             |
| Grade 1     | 51 26         | 15             | 6              |
| Grades 2 and 3 | 14 17       | 10             | 4              |
| 45 to <55 years | 297 243   | 107            | 93             |
| Underweight | 8 1           | 1              | 0              |
| Normal      | 174 127       | 58             | 49             |
| Grade 1     | 91 83         | 32             | 6              |
| Grades 2 and 3 | 24 31       | 16             | 13             |
| 55 to <65 years | 415 349  | 150            | 106            |
| Underweight | 2 3           | 2              | 0              |
| Normal      | 203 160       | 69             | 53             |
| Grade 1     | 156 138       | 52             | 43             |
| Grades 2 and 3 | 51 48       | 28             | 10             |

aBody mass index (BMI) at 5 years prior to diagnosis/reference date where BMI categorised as underweight: < 18.5 kg m\(^{-2}\); normal: 18.5 – 24.99 kg m\(^{-2}\); grade 1 overweight: 25 – 29.99 kg m\(^{-2}\); grades 2 and 3 overweight: ≥ 30 kg m\(^{-2}\) (WHO Expert Committee on Physical Status, 1995). BMI was missing for four cases and three controls as weight was not reported. bNHL = Non-Hodgkin’s lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma. Odds ratios adjusted for age, sex and region estimated using unconditional logistic regression.
SNPs were not statistically significant. LEP 19G/A and LEP –2548G/A among controls, with estimated haplotype frequencies of –2548G/19A, 41.5%; –2548G/19G, 18.5%; –2548A/19G, 39.2%; and –2548A/19A, 0.8%, were in linkage disequilibrium (D = 0.95), but despite the individual SNP effects, no associations between haplotypes and either NHL as a whole or FL in particular emerged.

Risks associated with BMI among interviewed and genotyped subjects were similar, with the OR of NHL among the 593 cases and 754 controls who were genotyped being 1.2 (95% CI 0.9 – 1.5, P = 0.16) and 1.4 (95% CI 1.0 – 2.0, P = 0.08) for being grade 1 and grades 2 or 3 overweight, respectively. To assess whether the risk associated with the energy homeostasis polymorphisms differed by BMI, analyses were repeated stratifying the genotyping data by BMI, and patterns for FL were less consistent. Non-Hodgkin’s lymphoma, and particularly DLBCL, is more common in men than women and the incidence increases with age above 25 years (Clarke and Glaser, 2002; Cartwright et al, 2005). Our observation for DLBCL in young men is based on small numbers, but if real, could reflect the effects of weight gain early in adulthood. Not only does body fat, and hence BMI, increase with age, but the site of fat deposition may also be important – men being most likely to accumulate abdominal fat than women (WHO Consultation on Obesity, 2000). Better markers of central, rather than total, adiposity would be waist circumference or waist-to-hip ratio (WHO Consultation on Obesity, 2000), which, up to now, have only been reported in one study of women, but no association with NHL was found (Cerhan et al, 2002). If weight gain in early adulthood is not responsible, our results could instead suggest that obesity from childhood is a risk factor for NHL. It seems unlikely however that nutrition during childhood, linked to adult stature (Silventoinen, 2003), increases NHL risk, since generally little evidence of an association with height has been presented either here or elsewhere (Whitemore et al, 1985; La Vecchia et al, 1990; Zhang et al, 1999; Cerhan et al, 2002). Alternatively, it may be that an underlying genetic component of obesity is involved in the pathogenesis of NHL.

Leptin, an adipokine which circulates at levels proportional to adipose tissue mass, regulates immune function as well as nutritional status (Otero et al, 2005). As circulating levels increase, leptin acts to modulate food intake, but in obesity, its rise with

| SNP | Control | NHL | DLBCL | FL |
|-----|---------|-----|-------|----|
| LEP 19G/A | 754 | 593 | 270 | 210 |
| GG | 275 | 235 | 104 | 1 |
| AG | 357 | 276 | 123 | 0.9 |
| AA | 122 | 79 | 43 | 0.9 |
| LEP –2548G/A | 260 | 170 | 81 | 1 |
| GG | 348 | 294 | 128 | 1.2 |
| GA | 145 | 127 | 59 | 1.3 |
| APM1 276G/T | 224 | 188 | 88 | 1 |
| QQ | 387 | 306 | 144 | 1.0 |
| RR | 133 | 99 | 38 | 0.8 |
| LEP –2548G/A | 398 | 341 | 158 | 1 |
| GG | 311 | 216 | 96 | 0.8 |
| TT | 45 | 35 | 16 | 0.9 |

Table 4 Number of cases and controls, adjusted odds ratios, and 95% confidence intervals for energy homeostasis polymorphisms

DISCUSSION

Here we present evidence that obesity and variants in the LEP gene may be important in the pathogenesis of NHL. Specifically, we found an association between NHL and excess adiposity estimated using BMI 5 years prior to diagnosis in both men and women, with a greater risk found among patients diagnosed at younger ages (<45 years). Risks were elevated for the two most common NHL subtypes, but the association remained statistically significant only for DLBCL. In contrast, the LEP 19G/A and LEP –2548G/A polymorphisms altered the risk of FL, particularly among men. These SNPs were not associated with risk of DLBCL and, generally, no associations were observed for LEP 223Q/R and APM1 276G/T. Given the increasing obesity and lymphoma rates worldwide, our findings may have important public health implications.

While several studies have suggested that the risk of NHL associated with BMI varies little with age and sex (Holly et al, 1999; Calle et al, 2003; Pan et al, 2004; Chang et al, 2005), our study is the first to examine risk by disease subtype, sex and age. With respect to the former, we, like others (Cerhan et al, 2002; Skibola et al, 2004; Chang et al, 2005), found that the risk of DLBCL rose with increasing BMI, but patterns for FL were less consistent. Non-Hodgkin’s lymphoma, and particularly DLBCL, is more common in men than women and the incidence increases with age above 25 years (Clarke and Glaser, 2002; Cartwright et al, 2005). Our observation for DLBCL in young men is based on small numbers, but if real, could reflect the effects of weight gain early in adulthood. Not only does body fat, and hence BMI, increase with age, but the site of fat deposition may also be important – men being most likely to accumulate abdominal fat than women (WHO Consultation on Obesity, 2000). Better markers of central, rather than total, adiposity would be waist circumference or waist-to-hip ratio (WHO Consultation on Obesity, 2000), which, up to now, have only been reported in one study of women, but no association with NHL was found (Cerhan et al, 2002). If weight gain in early adulthood is not responsible, our results could instead suggest that obesity from childhood is a risk factor for NHL. It seems unlikely however that nutrition during childhood, linked to adult stature (Silventoinen, 2003), increases NHL risk, since generally little evidence of an association with height has been presented either here or elsewhere (Whitemore et al, 1985; La Vecchia et al, 1990; Zhang et al, 1999; Cerhan et al, 2002). Alternatively, it may be that an underlying genetic component of obesity is involved in the pathogenesis of NHL.
increasing body fat has limited effect on satiety, suggesting negative regulators of leptin and insulin signalling, such as leptin receptor and adiponectin, are present (Bell et al, 2005). In the absence of measured plasma levels before the diagnosis of NHL, long-term variation in production of these adiponectins may be indicated by the polymorphisms investigated here, since the LEP 19G, LEP 2548A and LEPR 223R alleles have been associated with elevated leptin levels, and the APM1 276T allele with lower adiponectin levels (Hoffstedt et al, 2002; van Rossum et al, 2003; Filippi et al, 2004). Further, these polymorphisms have been linked with an obese phenotype in some Caucasian populations (Li et al, 1999; Mammes et al, 2000; Quinton et al, 2001; Yiannakouris et al, 2001; Nieters et al, 2002; Filippi et al, 2004; Jiang et al, 2004). Previously, Skibola et al (2004) reported that, relative to the LEP 19AA genotype, carriers of the LEP 19G allele were at increased risk of NHL, particularly FL (OR = 1.9, 95% CI 1.0 – 3.6). Using LEP 19GG as the referent group, the recalculated FL risk estimate for the LEP 19AA genotype is 0.6 (95% CI 0.3 – 1.3), similar to the OR of 0.5 (95% CI 0.3 – 0.8) presented here. As has been observed elsewhere, the BMIs of our controls were not correlated with LEP 19G > A (ρ = 0.014, P = 0.70) (Karvonen et al, 1998; Lucantoni et al, 2000), LEP 2548G > A (ρ = 0.013, P = 0.72) (Mammes et al, 1998; Le Stunff et al, 2000), LEPR 223Q > R (ρ = 0.008, P = 0.83) (Gotoda et al, 1997; Rosmond et al, 2000; Wauters et al, 2001) or APM1 276G > T (ρ = 0.024, P = 0.51) (Menzaghi et al, 2002; Fumeron et al, 2004). Moreover, this and the previous report by Skibola et al found little evidence that risks associated with BMI varied by genotype.

Obesity can induce a state of leptin and insulin resistance, chronic low-grade inflammation, and increased leptin, tumor necrosis factor (TNF)-α, IL-6 and C reactive protein serum levels (Marti et al, 2001). These proinflammatory mediators can activate a number of signalling pathways including nuclear factor (NF)-κB, transducer and activator of transcription (STAT) pathways. Most of matrix metalloproteinases and tissue inhibitors of metalloproteinases, which are associated with aggressive disease, neo- plastic growth and angiogenesis in B-cell lymphomas.

This study has a high level of case ascertainment and diagnostic confirmation. As with all case–control studies of this type, however, the possibility that the findings may reflect bias in the case and/or control populations needs to be considered. In our study, participants who resided in affluent areas were, on average, of smaller stature and greater BMI than those who resided in deprived areas. This pattern agrees with that seen in most national surveys (Joint Health Surveys Unit, 2003), and it is possible that the increased risks may have arisen from differential case–control participation. However, adjustment for deprivation did not alter the risk estimates for height or BMI. A further limitation relates to the self-reported nature of the anthropometric data analysed. Compared to a sample of the British population with anthropometric measurements (National Center for Social Research, 2004), our controls were taller and lighter, leading to a reduction in their derived BMI. It is, however, unlikely that cases estimated their height and weight differently from controls, as the hypothesis that obesity is related to NHL is not widely known.

In conclusion, our findings raise the possibility that obesity may increase risk of NHL as a whole, and DLBCL risk in particular. Our findings were most marked among men and those diagnosed at a comparatively young age (<45 years). Although the SNPs involved in energy homeostasis investigated in our study did not modify the risk of NHL associated with obesity, independent effects were seen for FL with the LEP 19G > A and LEP 2548G > A SNPs, irrespective of adiposity. Previous reports of NHL and BMI have been inconsistent, with little investigation of disease subtypes. New initiatives, aimed at pooling data from studies around the world including the one reported here (Boffetta et al, 2003), will hopefully provide further insight into the association between lymphoma and BMI.

ACKNOWLEDGEMENTS

This work was supported by the Leukaemia Research Fund of Great Britain, NIH Grant RO1-CA104862 from the US National Cancer Institute (MT Smith, PI) and by the National Foundation for Cancer Research. We thank all consultants, hospital staff, general practitioners and interviewees who participated in the study. Our thanks also go to Andrew Jack and Bridget Wilkins for confirming the patients’ diagnoses, Sara Rollinson and Heather Kesby for sample management and DNA extraction, and to the study staff.

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British Journal of Cancer (2005) 93(7), 811 – 816
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