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Common genetic variation within *IGFI*, *IGFII*, *IGFBP-1*, and *IGFBP-3* and endometrial cancer risk

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Abstract

Objective—The insulin-like growth factor (IGF) pathway plays a critical role in the growth and development of the uterus and is believed to function as a mediator of steroid hormone actions in the endometrium. The local expression of genes encoding IGFs and IGF-binding proteins (IGFBPs) are important in determining IGF bioactivity in the uterus. Genetic variation in key genes within the IGF pathway may influence the rate of cellular proliferation and differentiation in the uterus and ultimately affect the risk of endometrial cancer. Our hypothesis is that variant alleles in key genes involved in the IGF pathway will influence the development of endometrial cancer.

Methods—We conducted a case-control study nested within the Nurses' Health Study (NHS) and the Women's Health Study (WHS) to investigate the association between forty-four polymorphisms within *IGFI*, *IGFII*, *IGFBP-1*, and *IGFBP-3* with endometrial cancer risk using 692 invasive endometrial cancer cases and 1723 matched controls. We used conditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to assess the risk of endometrial cancer.

Results—We observed an inverse association with *IGFII* rs3741211 and endometrial cancer risk (OR = 0.79 (95% CI: 0.63, 0.99)) and *IGFII* rs1004446 and endometrial cancer risk (OR = 0.80 (95% CI: 0.68, 0.94)). We also observed an inverse association with *IGFBP-3* rs2453839 and endometrial cancer risk (OR = 0.81 (95% CI: 0.67, 0.98)). However, we did not observe any statistically significant associations with the polymorphisms in *IGFI* and *IGFBP1* and endometrial cancer risk.

Conclusions—Genetic variation with *IGFII* and *IGFBP-3* may influence endometrial cancer risk in Caucasians. Polymorphisms in *IGFI* and *IGFBP-1* were not associated with endometrial cancer risk, but further research is needed.

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Keywords

endometrial cancer; polymorphisms; genetics; IGF

Introduction

The insulin-like growth factor pathway plays a critical role in the growth and development of the uterus. Insulin-like growth factors (IGFs) are potent mitogenic and anti-apoptotic molecules involved in the regulation of cell proliferation and steroid hormone actions in the endometrium [1]. IGF-binding proteins (IGFBPs) are expressed in the uterus [2] and modulate the biological actions of IGF by regulating the availability of circulating IGF to target tissues and the binding of IGF to its receptors [3]. Only unbound IGF is biologically active [4], and therefore increased amounts of unbound IGF may lead to uncontrolled cellular proliferation in the uterus and may ultimately lead to the development of endometrial cancer. Local expression of genes encoding IGFs and IGFBPs are important in determining the level of bioactivity in the uterus.

IGF-I and IGF-II are expressed in virtually all tissues including the uterus [5]. Endometrial stromal cells produce IGF-I and IGF-II and their binding proteins (IGFBPs) [6]. IGF-I has effects on ovarian and testicular sex steroid synthesis, and together with insulin, has a key role in regulating the synthesis of sex hormone binding globulin [7]. Furthermore, IGF-I is able to act as a mitogen in uterine cells by increasing the cell number and proliferation rate. IGF-II mediates progesterone's effects in the secretory phase of the menstrual cycle [6], and has a critical role in endometrial differentiation [6] and in endometrial-embryo interactions [8]. IGFs are also potent simulators of endometrial cancer cell growth *in vitro* [9], and levels of IGF-I receptor and IGF-II receptor mRNA are increased in endometrial cancer samples compared to normal endometrium samples [10, 11]. IGF-I may regulate tumor growth not only through its receptor but as a local mediator of the growth-promoting action of estrogen in the uterus.

The biological actions of IGF are modulated by IGF-binding proteins (IGFBPs) [12]. More than 99% of the circulating IGFs are bound to IGFBPs, and over 75% of circulating IGFs are bound to IGFBP-3. Most IGF-I and IGF-II are found in a ternary complex with IGFBP-3 and the acid-labile subunit. Circulating IGFBP-3 prolongs the half-life of IGF in serum and limits the availability of free IGF [3]. High levels of IGFBP-3 are associated with reduced levels of IGF-I influencing the rate of cellular proliferation. The most abundant binding protein in the human endometrium is IGFBP-1 [6]. IGFBP-1 gene expression in the uterus is inhibited by insulin [13, 14] and stimulated by progesterone [2, 6, 13]. IGFBP-1 inhibits IGF receptor binding and the physiological actions of IGF in the uterus [15, 16]. Clinical conditions associated with an increased risk of endometrial cancer (e.g. polycystic ovaries, obesity, infertility) are also characterized by the absence or decreased expression and secretion of IGFBP-1 [2]. *In vivo* and *in vitro* studies have suggested that low levels of IGF-I and increased levels of IGFBP-1 inhibit both endometrial epithelial and stromal cell proliferation [6]. Therefore, in the decreased expression or absence of IGFBPs, the bioavailability and functional activity of IGF in the uterus may increase.

Heritability studies have demonstrated that approximately 40 to 80% of variation in IGF-I and IGFBP-3 levels may be (co-)determined by genetic factors [17-21]. Plasma levels of IGFs and IGFBPs vary widely in adults [22], and epidemiological studies suggest that individuals with elevated levels of IGF-I and decreased levels of IGFBP-3 levels have an increased cancer risk [3, 23-26]. A recent meta-analysis of five studies observed no association with IGFI levels and endometrial cancer risk [26]. Although research to identify

genetic determinants of IGF/IGFBP activity is intensifying, no studies have been conducted to investigate the association between polymorphisms within the IGF pathway and endometrial cancer risk.

Polymorphisms in genes involved in the IGF pathway may change gene expression and/or protein function, which may ultimately influence endometrial cancer risk. Our hypothesis is that variant alleles in key genes involved in the IGF pathway will influence the development of endometrial cancer. We conducted a case-control study nested within the Nurses' Health Study (NHS) and the Women's Health Study (WHS), to investigate the association between polymorphisms in *IGFI*, *IGFII*, *IGFBP-1*, and *IGFBP-3* with endometrial cancer risk, using 692 invasive endometrial cancer cases and 1723 matched controls.

Materials and Methods

The NHS is a prospective cohort study of 121,700 women enrolled in 1976. During 1989-90, blood samples were collected from 32,826 women. In 2000-2002, buccal cell samples were collected from 33,040 women who had not provided a blood sample. Cases were women with pathologically confirmed invasive endometrial cancer diagnosed after cohort inception and prior to June 1, 2004. The vast majority of our endometrial cancer cases in the NHS nested endometrial cancer case-control are adenocarcinomas (93.6%) followed by leiomyosarcoma (1.8%), squamous (1.8%), clear cell (1.4%), endometrial stromal sarcoma (0.9%), and undifferentiated (0.2%) cancer types. Controls were randomly selected from participants who had not had a hysterectomy and were free of diagnosed cancer up to and including the questionnaire cycle in which the case was diagnosed. Controls were matched to cases 3:1 or 2:1 according to year of birth, menopausal status at blood draw and at the cycle prior to diagnosis, and postmenopausal hormone use at time of blood draw (current versus not current users), and type of biospecimen. There were 555 NHS cases and 1312 NHS matched controls. Completion of the self-administered questionnaire was considered to imply informed consent, and written informed consent was received for the biospecimen samples.

The WHS is a completed randomized, double-blind, placebo-controlled trial investigating the benefits and risks of aspirin and vitamin E in the primary prevention of cancer and cardiovascular disease among 39,876 female health professionals, with enrollment starting in September 1992 and randomization beginning in April 1993 [27-29]. Blood samples were collected from 28,345 women. WHS cases consisted of women with confirmed endometrial cancer diagnosed after blood collection and prior to June 1, 2002. The majority of the endometrial cancer cases in the WHS are endometrioid adenocarcinomas (86.1%) followed by papillary serous adenocarcinoma (2.6%), mixed Mullerian tumor (2.6%), adenocarcinoma with squamous metaplasia (1.4%). Controls were randomly selected participants who had given a blood sample, had not had a hysterectomy, and were free of diagnosed cancer. Controls were matched to cases 3:1 according to age, menopausal status and postmenopausal hormone use. There were 137 WHS cases and 411 WHS matched controls. Written informed consent was obtained from all women before entry into the trial. Each study protocol was approved by the Committee on Use of Human Subjects of the Brigham and Women's Hospital, Boston, MA.

Genotyping

We genotyped *IGFI*, *IGFII*, *IGFBP1* and *IGFBP3* haplotype-tagging single nucleotide polymorphisms (htSNPs) identified by the Breast and Prostate Cancer Cohort Consortium (<http://ccnt.hsc.usc.edu/MECGenetics/>) [20, 30, 31]. Their method of htSNP selection has been previously described [32]. In Caucasians, 14 htSNPs were selected in four haplotype blocks for the *IGFI* gene and 13 htSNPs were selected in three haplotype blocks across the

IGFBP1 and *IGFBP3* genes based on a correlation of .080 between the true haplotypes and estimated haplotype probabilities (R²_h) for each participant. In *IGFBP1* and *IGFBP3*, two additional SNPs were identified that did not fall into haplotype blocks. For the *IGFII* gene, 8 htSNPs were selected, and 7 additional SNPs were also identified that did not fall into haplotype blocks. Due to poor genotyping success of *IGFII* rs4529869, we selected an alternate SNP (rs3213221). DNA extraction and genotyping were performed at the Dana–Farber Cancer Institute/Harvard Cancer Center High Throughput Genotyping Core, a unit of the Harvard–Partners Genotyping Facility. DNA was extracted from buffy coat and buccal cell samples using a QIAamp 96 DNA Blood Kit (Qiagen). Genotyping assays for all 44 SNPs were performed either by Biotrove OpenArray® Real-Time qPCR system (Woburn, MA) or by the 5' nuclease assay (Taqman) on the Applied Biosystems Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). Genotyping was performed by laboratory personnel blinded to case–control status, and 5% blinded duplicate quality control samples were inserted to validate genotyping procedures; concordance for blinded samples was 100%. The percentage of missing genotyping data was <5%.

Statistical analysis

We compared genotype distributions in cases and controls, and genotype frequencies were tested for Hardy–Weinberg equilibrium. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by conditional logistic regression to assess the association of *IGFI*, *IGFII*, *IGFBP-1*, *IGFBP-3* genotypes with endometrial cancer risk. Individuals homozygous for the more common allele served as the reference category. In addition to the matching factors, analyses were adjusted for body mass index (BMI; kg/m²); age at menarche; parity/age at first birth; smoking status; menopausal status at diagnosis; age at menopause; and postmenopausal hormone use at diagnosis. Tests of heterogeneity were conducted to determine the appropriateness of pooling the two datasets. We used the DerSimonian and Laird random effects model to combine results from the two cohorts after testing for heterogeneity. Because of the limited numbers of non-Caucasian subjects, we elected to perform our analyses using only cases and matched controls from Caucasian women. Numbers may vary for the different analyses due to missing genotype data. All *P* values are two-sided; *P* values < 0.05 were considered statistically significant. We used the SAS Version 9.1 software (SAS Institute, Cary, NC).

We employed a haplotype-based approach for *IGFI*, *IGFII*, *IGFBP1*, and *IGFBP3* and estimated haplotype frequencies and haplotype-specific ORs using an expectation–substitution method to account for haplotype uncertainty given unphased genotyping data [33, 34]. Haplotypes with less than 5% frequency were grouped together. We performed a global test of significance to determine whether haplotype frequencies differed between cases and controls. Conditional logistic regression was used to calculate adjusted ORs and 95% CIs for haplotype associations with endometrial cancer risk, using the most common haplotype as the reference category.

Results

The complete nested case-control study consisted of 692 endometrial cancer cases and 1723 matched controls. For this study, participants were restricted to women of European ancestry leaving 549 NHS endometrial cancer white cases and 1,288 matched white controls (*n* = 244 cases and 479 controls from the NHS buccal cell cohort and 305 cases and 479 controls from NHS blood cohort), and 130 WHS endometrial cancer white cases and 391 matched white controls for a total sample size of 679 cases and 1,679 matched controls. Descriptive characteristics of the two study populations have been previously published [35] (Supplementary Table 1). Allele frequencies were similar to previous reports in Caucasian populations (Table 1) [36, 37], and genotypes were in accordance with Hardy–Weinberg

equilibrium. P-values for the tests of heterogeneity comparing the NHS and WHS results were >0.05, except for six SNPs.

We did not observe any statistically significant associations with the polymorphisms in *IGFI* and *IGFBP1* and endometrial cancer risk (Table 2). We did observe an inverse association with *IGFBP-3* rs2453839 and endometrial cancer risk (OR = 0.81 (95% CI: 0.67, 0.98) (Table 2). We also observed an inverse association with *IGFII* rs3741211 and endometrial cancer risk (OR = 0.79 (95% CI: 0.63, 0.99)) and *IGFII* rs1004446 and endometrial cancer risk (OR = 0.80 (95% CI: 0.68, 0.94)) (Table 3). We did not observe any significant associations between haplotypes and endometrial cancer risk (data not shown). We did not perform gene-environment interactions as there is no prior biological evidence to suggest that the SNPs may interact differently with varying levels of environmental exposures.

Discussion

Polymorphisms that change gene expression or protein function might result in a relative increase or decrease in circulating IGF or IGFBP levels and may influence endometrial cancer risk. We have chosen to focus our efforts on key genes in the IGF pathway that are most relevant and important to the development of endometrial cancer risk. This is the first study to comprehensively evaluate variation in the *IGFI*, *IGFII*, *IGFBP1*, *IGFBP3* genes and endometrial cancer risk. In our pooled analyses, we observed an inverse association with *IGFII* rs3741211 (OR = 0.79 (95% CI: 0.63, 0.99)), *IGFII* rs1004446 (OR = 0.80 (95% CI: 0.68, 0.94)), and *IGFBP-3* rs2453839 (OR = 0.81 (95% CI: 0.67, 0.98)) and endometrial cancer risk. These significant associations were not consistently observed in the individual cohorts, therefore these results should be interpreted with caution. We did not observe any statistically significant associations with the polymorphisms in *IGFI* and *IGFBP1* and endometrial cancer risk. The results from this study suggest that common genetic variants in the *IGF-I* and *IGFBP1* genes do not play a significant role in endometrial cancer risk among Caucasian women, yet the role of *IGFII* and *IGFBP-3* SNPs needs to be further elucidated.

Recent studies have investigated the associations of the investigated *IGFI*, *IGFBP1*, and *IGFBP3* polymorphisms and breast cancer risk [20], ovarian cancer risk [36], and mammographic density [37]. The Breast and Prostate Cohort Consortium (BPC3) genotyped the same *IGFI*, *IGFBP1*, and *IGFBP3* SNPs in 6,912 breast cancer cases and 8,819 matched controls and observed no statistical associations between these SNPs and breast cancer risk, however they did observe significant associations between several *IGFBP3* SNPs and IGFBP3 plasma levels and *IGFI* SNPs and IGF1 plasma levels [20]. The BPC3 did observe an association with IGFBP-3 levels and the *IGFBP-3* rs2453839 [20], which we observed had an inverse association with endometrial cancer risk. The association between rs2453839 and IGFBP-3 levels was also observed by D'Aloisio *et al.* [38]. In a cross-sectional study of 1,121 control subjects, Tamimi *et al.* [37] concluded that genetic variation within *IGFI* was strongly associated with mammographic density. In a pooled analysis, Terry *et al.* [36] identified several SNPs in the IGF pathway that were associated with ovarian cancer risk and plasma IGF1, IGFBP2, and IGFBP3 levels. None of these studies investigated the significance of *IGFII* genetic variation and disease risk.

IGFII is a potent mitogen and involved in the regulation of epithelial cell proliferation. We observed an inverse association with *IGFII* rs1004446 and *IGFII* rs3741211 and endometrial cancer risk. Concannon *et al.* using genome-wide linkage scan data and family-based association methods identified rs1004446 as displaying evidence of association with type 1 diabetes at a genome-wide significance level ($P = 2.5 \times 10^{-9}$) [39]. In this study, 2,496 families with type 1 diabetes were genotyped with a panel of 6,090 SNPs. Significant results were followed up by genotyping in two independent sets of samples: 2,214 parent-affected

child trio families and a collection of 7,721 cases and 9,679 controls. Type 1 and type 2 diabetes have been consistently associated with an increased risk of endometrial cancer [40, 41]. Plasma insulin levels have a complex relationship with levels of IGFs and IGFBPs [42, 43]. Studies have demonstrated that elevated IGFII is associated with obesity [44-46]; obesity is a strong risk factor for endometrial cancer and type 2 diabetes. Two case-control studies have also observed increased levels of IGFII among endometrial cancer cases compared to controls [47, 48]. It is possible that the observed associations between the two *IGFII* polymorphisms and endometrial cancer risk may be due to the relationship of IGFII with obesity and diabetes.

Our study is the first prospective case-control study to investigate these 44 SNPs in relation to endometrial cancer risk. One of the main strengths of this study is its comprehensive and systematic approach to characterizing variation in *IGFI*, *IGFII*, *IGFBP-1*, and *IGFBP-3*. We selected tagging SNPs across the 4 genes in order to provide sufficient coverage across the genes. The use of the NHS and WHS allowed us the opportunity to replicate the observed associations between these polymorphisms and endometrial cancer risk simultaneously in two large, well-defined cohorts. This analysis was restricted to Caucasians only, and therefore the results of this study can only be generalized to Caucasians. To assess the power of our study, we conducted power calculations using Quanto [49]. The large sample size provided sufficient power ($\geq 80\%$) to detect a minimum odds ratio of ≥ 1.25 in the pooled analysis (assuming minor allele frequency $\geq 10\%$; $\alpha = 0.05$ on the log-additive scale; two-sided test; and a matched case-control study design). Differences in cohort-specific and pooled effect estimates and statistical significance may be the result of differences in power due to changes in sample size. We may have limited power to detect minor to modest genotype-disease associations; therefore, such associations cannot be ruled out. We also cannot rule out the possibility that some genetic variants may exert their effect through interactions with genetic polymorphisms in other genes or certain lifestyle factors. These interactions can be addressed in future studies with larger sample sizes, and after functional studies have determined the significance of the polymorphisms. The relationships between sex steroid hormones and the insulin-like growth factor pathway may help to identify important components in endometrial cancer initiation and progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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7. Research Highlights

- Select *IGF-I* and *IGFBP1* polymorphisms not associated with endometrial cancer risk
- Select *IGFII* and *IGFBP-3* SNPs are inversely associated with endometrial cancer risk
- IGF pathway may play role in endometrial cancer development

Table 1*IGFI*, *IGFII*, *IGFBP1*, and *IGFBP3* SNPs in the NHS and WHS

Gene	SNP ID	Minor allele frequency ^I		Nucleotide change
		NHS	WHS	
IGFI				
	rs7965399	0.04	0.05	C/T
	rs35767	0.17	0.17	A/G
	CV11752586	0.23	0.20	A/G
	rs1019731	0.13	0.14	A/C
	rs2195239	0.24	0.24	C/G
	CV346219	0.28	0.29	A/G
	rs2373722	0.07	0.07	A/G
	rs1549593	0.16	0.13	G/T
	rs1520220	0.18	0.20	C/G
	CV2801104	0.13	0.15	G/C
	rs2946834	0.32	0.36	G/A
	rs4764876	0.25	0.28	C/G
	rs4764695	0.50	0.48	A/G
	rs1996656	0.18	0.19	A/G
IGFBP1 and IGFBP3				
	CV395979	0.30	0.36	A/G
	rs1553009	0.21	0.17	A/G
	CV395975	0.23	0.24	G/C
	rs2201638	0.04	0.05	A/G
	rs1065780	0.40	0.37	G/A
	rs4988515	0.04	0.04	C/T
	rs4619	0.37	0.34	A/G
	rs1908751	0.29	0.33	C/T
	rs2270628	0.20	0.18	C/T
	rs3110697	0.41	0.43	A/G
	rs2854746	0.42	0.38	G/C
	rs2854744	0.43	0.44	T/G
	rs2132570	0.22	0.23	T/G
	rs6670	0.23	0.19	T/A
	rs2453839	0.21	0.23	T/C
IGFII				
	rs4261263	0.36	0.38	A/C
	rs680	0.26	0.28	C/T
	rs3213221	0.38	0.36	C/G

Gene	SNP ID	Minor allele frequency ¹		Nucleotide change
		NHS	WHS	
	rs734351	0.39	0.35	A/G
	rs3741208	0.38	0.41	A/G
	rs3741205	0.27	0.24	A/C
	rs1004446	0.38	0.37	A/G
	rs4320932	0.21	0.18	C/T
	rs7924316	0.45	0.44	G/T
	rs3842748	0.22	0.22	C/G
	rs2070762	0.50	0.46	A/G
	rs4244809	0.20	0.20	A/G
	rs4366464	0.07	0.08	C/G
	rs1003483	0.49	0.51	G/T
	rs3741211	0.38	0.37	A/G

¹ Restricted to white controls.

Table 2

Association between polymorphisms in the *IGF1*, *IGFBP1*, and *IGFBP3* genes and endometrial cancer risk in the NHS and the WHS

Gene SNP	rs number	NHS OR (95% CI) ^{1,2,3}	WHS OR (95% CI) ^{1,2,3}	Pooled OR (95% CI) ^{1,2,3}	p het
<i>IGF1</i>					
	rs7965399	0.83 (0.53, 1.30)	0.55 (0.22, 1.39)	0.77 (0.51, 1.15)	0.43
	rs35767	1.03 (0.81, 1.30)	0.58 (0.33, 1.03)	0.82 (0.47, 1.42)	0.07
	CV11752586	0.85 (0.69, 1.04)	1.50 (0.96, 2.34)	1.09 (0.62, 1.90)	0.02
	rs1019731	0.99 (0.77, 1.28)	1.50 (0.90, 2.52)	1.15 (0.78, 1.69)	0.16
	rs2195239	0.94 (0.78, 1.14)	1.48 (0.97, 2.26)	1.14 (0.73, 1.76)	0.06
	CV346219	1.05 (0.87, 1.27)	1.30 (0.86, 1.97)	1.09 (0.92, 1.29)	0.36
	rs2373722	1.24 (0.89, 1.71)	0.69 (0.33, 1.44)	1.02 (0.59, 1.75)	0.16
	CV2801104	1.16 (0.90, 1.50)	0.52 (0.28, 0.96)	0.82 (0.37, 1.80)	0.02
	rs1549593	0.92 (0.72, 1.16)	1.92 (1.19, 3.11)	1.29 (0.62, 2.66)	0.006
	rs1520220	1.03 (0.83, 1.29)	1.18 (0.77, 1.80)	1.06 (0.87, 1.30)	0.58
	rs2946834	1.11 (0.93, 1.34)	0.96 (0.66, 1.39)	1.08 (0.92, 1.27)	0.47
	rs4764876	1.16 (0.95, 1.40)	1.10 (0.73, 1.65)	1.15 (0.96, 1.36)	0.83
	rs4764695	0.92 (0.78, 1.09)	1.08 (0.74, 1.59)	0.94 (0.81, 1.10)	0.45
	rs1996656	1.07 (0.86, 1.32)	1.40 (0.88, 2.22)	1.13 (0.91, 1.39)	0.30
<i>IGFBP1</i>					
	CV395979	0.99 (0.82, 1.20)	0.63 (0.42, 0.93)	0.81 (0.52, 1.27)	0.04
	rs1553009	1.12 (0.91, 1.37)	1.23 (0.79, 1.93)	1.14 (0.94, 1.37)	0.69
	CV395975	0.96 (0.78, 1.18)	0.98 (0.66, 1.45)	0.96 (0.80, 1.16)	0.92
	rs2201638	0.79 (0.49, 1.26)	0.19 (0.04, 0.82)	0.46 (0.12, 1.78)	0.07
	rs1065780	0.98 (0.82, 1.17)	0.99 (0.68, 1.45)	0.98 (0.84, 1.15)	0.94
	rs4988515	0.88 (0.58, 1.35)	0.60 (0.22, 1.63)	0.83 (0.56, 1.23)	0.49
	rs4619	0.95 (0.80, 1.13)	0.95 (0.66, 1.37)	0.95 (0.81, 1.11)	0.99
	rs1908751	0.90 (0.74, 1.10)	0.80 (0.56, 1.15)	0.88 (0.74, 1.04)	0.56
<i>IGFBP3</i>					
	rs2270628	0.93 (0.75, 1.15)	0.77 (0.48, 1.23)	0.90 (0.74, 1.09)	0.47

Gene SNP	rs number	NHS OR (95% CI) ^{1,2,3}	WHS OR (95% CI) ^{1,2,3}	Pooled OR (95% CI) ^{1,2,3}	p het
	rs6670	1.02 (0.83, 1.24)	1.99 (1.27, 3.11)	1.38 (0.72, 2.65)	0.008
	rs2453839	0.84 (0.68, 1.04)	0.67 (0.42, 1.07)	0.81 (0.67, 0.98)	0.39
	rs3110697	1.06 (0.89, 1.27)	1.07 (0.74, 1.56)	1.07 (0.91, 1.25)	0.96
	rs2854746	0.95 (0.80, 1.15)	1.08 (0.76, 1.55)	0.98 (0.83, 1.15)	0.54
	rs2854744	1.08 (0.90, 1.30)	1.03 (0.74, 1.43)	1.07 (0.91, 1.25)	0.79
	rs2132570	1.09 (0.88, 1.35)	0.95 (0.60, 1.52)	1.06 (0.88, 1.29)	0.61

¹ Restricted to Caucasians

² Conditional logistic regression model conditioned on the strata defined by the matching variables and body mass index at diagnosis, age at menarche, age at menopause, menopausal status and postmenopausal hormone use at diagnosis, parity, age at first birth, and smoking status.

³ Represents risk for a 1 unit increase in minor allele number.

Table 3

Association between polymorphisms in the *IGFII* gene and endometrial cancer risk in the NHS and the WHS

Gene SNP	rs number	NHS OR (95% CI) ^{1,2,3}	WHS OR (95% CI) ^{1,2,3}	Pooled OR (95% CI) ^{1,2,3}	p het
<i>IGFII</i>					
	rs3213221	1.08 (0.91, 1.29)	1.15 (0.79, 1.65)	1.09 (0.94, 1.25)	0.79
	rs4261263	1.19 (1.00, 1.41)	0.91 (0.63, 1.32)	1.10 (0.87, 1.39)	0.20
	rs680	1.04 (0.86, 1.26)	0.81 (0.54, 1.23)	0.99 (0.81, 1.20)	0.29
	rs734351	1.02 (0.85, 1.23)	1.15 (0.80, 1.67)	1.05 (0.88, 1.23)	0.56
	rs4244809	1.07 (0.87, 1.23)	0.93 (0.58, 1.50)	1.04 (0.86, 1.26)	0.62
	rs4366464	1.10 (0.80, 1.51)	1.34 (0.77, 2.36)	1.16 (0.88, 1.52)	0.55
	rs1003483	0.95 (0.81, 1.12)	1.24 (0.87, 1.77)	1.04 (0.82, 1.32)	0.19
	rs3741211	0.84 (0.71, 1.00)	0.65 (0.43, 0.97)	0.79 (0.63, 0.99)	0.24
	rs3741208	1.09 (0.92, 1.28)	1.33 (0.95, 1.87)	1.14 (0.96, 1.35)	0.29
	rs3741205	1.08 (0.89, 1.31)	1.30 (0.86, 1.97)	1.11 (0.94, 1.33)	0.43
	rs1004446	0.82 (0.69, 0.97)	0.69 (0.47, 1.04)	0.80 (0.68, 0.94)	0.46
	rs4320932	1.01 (0.82, 1.25)	1.23 (0.78, 1.93)	1.05 (0.86, 1.26)	0.44
	rs7924316	0.99 (0.84, 1.18)	0.84 (0.58, 1.22)	0.97 (0.83, 1.13)	0.43
	rs3842748	0.89 (0.68, 1.17)	0.44 (0.24, 0.80)	0.66 (0.33, 1.31)	0.03
	rs2070762	1.05 (0.89, 1.24)	0.94 (0.66, 1.34)	1.03 (0.88, 1.20)	0.59

¹ Restricted to Caucasians

² Conditional logistic regression model conditioned on the strata defined by the matching variables and body mass index at diagnosis, age at menarche, age at menopause, menopausal status and postmenopausal hormone use at diagnosis, parity, age at first birth, and smoking status.

³ Represents risk for a 1 unit increase in minor allele number.