(95% CI) = 0.51–0.89, $P = 0.006$). The *TGFBR2–875G>A* polymorphism frequencies for homozygous GG and GA/AA were 63% and 37% in PC group and 62% and 38% in the control group, respectively. We found lack of statistical significant association of *TGFBR2* genetic variants with PC risk (aOR = 1.05, 95% CI = 0.80–1.38, $P = 0.731$).

Conclusions: Our results show a protective effect associated with C allele (*TGFB1+869T>C*) for PC development. Functional polymorphisms that influence cellular microenvironment may help determine individual higher risk genetic profiles, which can impact PC diagnosis and chemoprevention strategies.

90 NQO1 polymorphism, maternal exposure and the risk of infant leukemia

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Introduction: Chromosomal abnormalities associated with infant leukemias (IL) originate during fetal life and often involve rearrangements of the *MLL* gene. The finding that similar abnormalities develop in children and adults treated with inhibitors of topoisomerase II (topo II) has led to the hypothesis that maternal exposure to topo II inhibitors, such as pesticides and benzene metabolites, during pregnancy might induce infant leukemias. NAD(P)H:quinone oxidoreductase 1 (NQO1) protects cells against oxidative stress and toxic quinones. A C609T polymorphism in the *NQO1* gene destabilizes and inactivates the enzyme and it has been reported as a susceptibility factor to IL. Taken together, infant and maternal genotypes of *NQO1*, in combination with exposure, could be important in etiology of IL. The aim of this study was to explore *NQO1* polymorphism in IAL with *MLL* translocation and, also evaluate mothers' genotypes in relation to different exposures during pregnancy.

Materials and Methods: The study population comprised 332 children (ages, 0−24 months-old), being 143 IL and 189 aged-matched controls. Samples from 177 mothers, who answered an epidemiological questionnaire, were also genotyped. Cases were diagnosed according to standard classifications. *MLL* characterization was done by reverse transcription-PCR and/or by fluorescence *in situ* hybridization. The *NQO1* C609T polymorphism was evaluated by PCR-RFLP. Statistical analyses were done using the SPSS 15.0 software. The differences in the genotype distribution between patients and controls, and across mothers of cases and controls were tested by logistic regression analysis to calculate ORs and 95% confidence intervals (CIs).

Results: Fifty eight percent of infants were positive for *MLL* rearrangements. We found the following CT + TT genotypes frequencies: 48.1% for controls and 45.4% for cases, whereas 47.8% for cases' mothers and 45.9% for controls' mothers. There was no difference across cases and controls in relation to *NQO1* genotypes frequencies [OR = 1.28; CI 95%, 0.82–1.99], nor even for mothers [OR = 1.93; CI 95%, 0.61–6.11]. Children with CT or TT genotypes didn't appear to be more prone to have *MLL* translocations [OR = 0.90; CI 95%, 0.43–1.86].

Conclusion: These preliminary results didn't show any association between *NQO1* polymorphism and *MLL* rearrangements. We noticed a higher CT + TT genotype frequency in cases' mothers but it is not statistically significant. Also, we observed that mothers who are exposed to hormones and pesticides during pregnancy have a higher risk to give birth to children who later developed leukemia. We believe that further analyses increasing the sample size may be able to demonstrate an association across mother's genotypes.

91 Analysis of BRIP1 in italian male breast cancer patients

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Background: Male breast cancer (MBC) is a rare disease compared to female breast cancer (FBC). MBC shares many similarities with FBC, including genetic predisposition factors such as *BRCA1/2* mutations. The frequency of *BRCA1/2* mutations ranges between 4 and 40% for *BRCA2* and up to 10% for *BRCA1* in different MBC series, thus suggesting the contribution of additional susceptibility genes.

Several studies identify *BRIP1* (BRCA1-interacting protein 1, also known as BACH1 and FANCJ) as a moderate-penetrance breast cancer (BC) susceptibility gene, accounting for about 1% of *BRCA1/2* negative familial/early-onset BCs. *BRIP1* encodes a DEAH helicase which interacts with the BRCT domain of BRCA1 and has BRCA1-dependent DNA repair and checkpoint functions. Interestingly, there are evidences that *BRIP1* might also play a role in susceptibility of prostate cancer, a tumour which may share risk factors with MBC. However, the role of *BRIP1* in MBC susceptibility is still unknown. In this study, we aimed to assess whether *BRIP1* alterations may contribute to MBC risk in Italy.

Material and Methods: We performed a mutational screening in 70 Italian MBC cases, negative for *BRCA1/2* mutations, selected from a population-based series of 123 MBCs. The complete coding region and intron-exon boundaries of *BRIP1* were analyzed by using SSCP (Single Strand Conformation Polymorphism). Cases displaying abnormal SSCP patterns were evaluated by direct sequencing. Statistical analysis was performed using the chi-square test.

Results: No truncating mutations were found. Two previously reported variants in the BRCT binding domain (E879E and P919S), and a neutral intronic variant (IVS4−28G>A) were identified. In order to evaluate the putative influence of the *BRIP1* P919S variant on MBC risk, we carried out a population-based case-control study based on a total of 97 MBC cases and 130 healthy adult male population controls from the same area. The frequency of the rare allele in cases was 36.2%, compared to 33.5% in population controls. No statistically significant difference in the distribution of the three specific *BRIP1* P919S genotypes was observed between MBC cases and controls ($p = 0.7$).

Conclusions: Overall, our results suggest that *BRIP1* do not play a major role in MBC susceptibility in Italy. However, larger studies are needed to explore its potential role as low risk gene.

92 Role of EGFR, HER2 and PIK3CA alterations in male breast cancer

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Background: EGFR and HER2 are tyrosine kinase receptors that activate different pathways, including PIK3-Akt, involved in cell proliferation, migration and survival. Thus EGFR, HER2 and PIK3 can play a relevant role in tumourigenesis, by mediating processes involved in neoplastic progression. *EGFR, HER2* and *PIK3* are frequently alterated in breast cancer (BC). EGFR and HER2 are amplified or over-expressed in about 20−40% of BC and mutations at their kinase domains are observed in about 2−4% of BC. Mutations at helical and kinase domains of *PIK3CA* gene, coding the catalitical subunity of PIK3, are reported in 8−40% of BC.

Male BC (MBC) is a rare and less investigated disease compared with female BC (FBC). Current knowledge on MBC biology is mainly derived from FBC. MBC shares many similarities with FBC, including genetic predisposition factors.

To date, the role of *EGFR*, *HER2* and *PIK3CA* alterations in MBC is very limited. Taking into account that EGFR, HER2 and PIK3CA have both prognostic and predictive value in BC, studies on the role of these genes could have important implications in the elucidation of pathogenetic mechanisms of MBC and in the clinical management of MBC patients.

Material and Methods: This study was performed on a series of 102 MBC cases characterized for clinicopathological features and *BRCA1*/*BRCA2* germ-line mutations. We have analyzed the presence of somatic mutations, amplification and expression of *EGFR*, *HER2* and *PIK3CA* by SSCP and automatic sequencing, qRT-PCR and IHC respectively.

Results: A mutation frequency of 4% was observed for *PIK3CA.* In our series *PIK3CA* common mutation (E545K) was identified in three different cases and a novel mutation (S553X) in one case. Interestingly, all tumours harboring *PIK3CA* mutations were ER+/PR+, in agreement with data obtained in FBC. Moreover *PIK3CA* resulted amplified with a frequency of 16%. No pathogenetic mutations were identified in *EGFR* and *HER2* genes but *EGFR* resulted amplified in 17% and HER2 over-expressed in 27.8% of cases and a statistical significant association emerged between HER2 over-expression and PR− ($p = 0.022$), MIB+ ($p = 0.028$), G3 ($p = 0.001$).

Conclusions: Our data indicate that alterations of *EGFR*, *HER2* e *PIK3CA* are involved in the pathogenesis of MBC at a comparable level as in FBC. Over-expression of HER2 allows the identification of a subgroup of MBC cases with specific pathological and biological characteristics indicative of aggressive clinical behavior.

93 Are variations in Helicobacter pylori cag pathogenicity island-genes associated with neoplastic progression in gastric cancer?

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Background: Helicobacter pylori is a bacterium that colonizes the human stomach and can establish a long-term infection of the gastric mucosa. Hp infection affects over 50% of the worldwide population, with a prevalence ranging from 20% in developed countries to over 90% in developing countries. Persistent Hp infection often induces gastritis and is associated

with the development of peptic ulcer disease, atrophic gastritis, and gastric adenocarcinoma. Virulent Hp isolates harbor the cag (cytotoxin-associated genes) pathogenicity island (cagPAI), a 40 kb stretch of DNA that encodes components of a type IV secretion system (T4SS). This T4SS forms a pilus for the injection of virulence factors into host target cells, such as the CagA oncoprotein. In a previous study a very strong association between current infection with cagA-positive Hp strains and the severity of gastric precancerous lesions has been showed.
Material and Methods: We analyzed the genetic variability in CagA and other selected genes of the Hp PAI, using DNA extracted from frozen gastric biopsies or from cultured strains from patients with gastric preneoplastic or cancer lesions. Patients where from Venezuela, Mexico and Paraguay, areas with high prevalence of Hp infection and gastric cancer. Because of the high genetic variability of the Hp genome, the study required a thorough optimization of the experimental conditions. Thus, sequencing reactions were carried out by both, Sanger and next-generation pyrosequencing (454 Roche) methods.
Results: Sequence analysis showed high variability in most of the cagPAI genes we have tested. In particular, the *cagA* gene showed striking ethnic and individual variation in its C-terminal region, where repetitive phosphorylation (EPIYA) motifs are located. We found different combinations of these biologically important EPIYA types.
Conclusions: This first analysis confirms the presence of high variability in the Hp PAI genes, which warrants further investigations for the risk of neoplastic progression within CagA positive patients.

94 Withdrawn

95 Associations between functional EGFR polymorphisms and glioma risk

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Background: The epidermal growth factor receptor (EGFR) regulates important cellular processes and is frequently implicated in human tumours. Somatic alterations of this receptor tyrosine kinase influence several mechanisms of malignant transformation and are common in gliomas. In addition, germline *EGFR* functional polymorphisms may have implications in carcinogenesis. Two single nucleotide polymorphisms (SNPs) were found in the essential promoter region (−216G/T and −191C/A) of the *EGFR* gene. The −216G/T has functional consequences, with the T allele being associated with higher promoter activity, resulting in increased gene expression both *in vitro* and *in vivo*. Additionally, a highly polymorphic microsatellite sequence $(CA)_n$ repeat in intron 1 of *EGFR* has been shown to be functional, as the transcriptional levels of *EGFR* decline with increasing numbers of $(CA)_n$ repeats. In the present study, we aimed to elucidate the roles of these *EGFR* polymorphisms in glioma susceptibility and prognosis.
Material and Methods: We conducted a case-control study with 245 glioma patients and 412 cancer-free controls from Portugal. Genetic variants of *EGFR* were determined by PCR-RFLP analysis (for −216G/T and −191C/A) or by PCR followed by single capillary genetic analysis [for $(CA)_n$ repeat]. Univariate and unconditional multivariate logistic regression models were used to calculate odds ratio (OR) and 95% confidence intervals (95% CI). A Cox-regression model was used to evaluate patient survival.
Results: The allele frequencies of −216G/T, −191C/A, and $(CA)_n$ repeat polymorphisms in the cancer-free control group in our study are similar to those previously reported in American Caucasian populations. Associations between *EGFR* −216G/T and −191C/A variants and glioma risk were not statistically significant ($p > 0.05$). Furthermore, no associations were found when glioma patients were stratified by histological types (*e.g.*, astrocytoma and oligodendroglioma). In contrast, shorter variants of the intron 1 $(CA)_n$ repeat conferred higher risks for gliomas, glioblastomas, and oligodendrogliomas ($P < 0.05$). No associations were observed between *EGFR* polymorphisms and patient outcomes.
Conclusions: Our data do not implicate *EGFR* −216G/T and −191C/A polymorphisms as risk factors for gliomas, but suggest the length of *EGFR* $(CA)_n$ repeat in intron 1 as a susceptibility factor for development of gliomas. Future studies are warranted to investigate how these *EGFR* genetic variants may affect therapeutic responses, particularly to EGFR-targeted therapies currently tested in clinical trials for glioma patients.

96 Adiponectin functional polymorphisms and haplotype are associated with prostate cancer aggressiveness and to hormonal castration resistance

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Background: Adipokines have been proposed as mediators in the association between obesity and prostate cancer (PCa). Recent findings described that higher prediagnostic adiponectin levels predispose men to a lower risk of developing high-grade prostate cancer. Functional polymorphisms and haplotypes in *ADIPOQ* gene (*ADIPOQ+45T>G*, *ADIPOQ+276G>T* and haplotype +45/+276) seem to influence adipoQ circulating levels.
Material and Methods: We conducted a prospective study in biopsy-proven PCa patients (n = 944). Patients were appropriately followed in the clinical setting for a median time of 39.4 months (3.2 to 231.5 months). Polymorphisms were genotyped through PCR-RFLP and Real Time-PCR. Haplotypes were derived from *ADIPOQ+45* and *ADIPOQ+276* genotypes and analysed according to the adiponectin production genetic profile.
Results: Results presented evidence that *TT* carriers of *ADIPOQ+276* had increased risk for higher Gleason score (OR = 1.99; 1.2−3.3 $p = 0.004$). In the polymorphism at locus +45 an association was observed between higher levels of testosterone at diagnosis and carrying GG genotype ($p = 0.012$). Univariate Kaplan-Meier function plots analysis showed a shorter time to hormonal castration resistance in TT carriers of *ADIPOQ+276G>T* polymorphism, when compared with G carriers (54.4 and 93.2 months, respectively; $p = 0.006$). Combined haplotypic analysis showed an increased risk for Gleason $\geqslant 8$ with high/intermediate *ADIPOQ* expression genetic profile (OR = 1.92, 95%CI: 1.3−2.8; $p = 3.7 \times 10^{-4}$). This genetic profile was also associated with a higher body mass index (BMI) ($p = 0.022$). Kaplan–Meier function plots analysis showed shorter time to hormonal castration resistance in high/intermediate, when compared with Low adiponectin producers (54.4 and 96.7 months, respectively; $p = 3.6 \times 10^{-4}$). After multivariate Cox Regression analysis, using as covariants stage of disease, Gleason score and PSA at diagnosis, the high/intermediate adiponectin producers evidenced an increased risk for developing resistance to hormonal castration (HR = 1.8, 95% CI: 1.1−2.9; $p = 0.027$).
Conclusions: Functional *ADIPOQ* genotypes and haplotypes that correlate with circulating adiponectin levels might be associated with genetic susceptibility for PCa aggressiveness and shorter progression-free interval during hormonal castration treatment.

97 Non-synonym leptin receptor genetic variants, prostate cancer susceptibility and aggressiveness

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Background: Leptin is a hormone synthesized preferentially in adipose tissue. Circulating levels are well correlated with obesity status while its receptor (LEPR) was found to be overexpressed in prostate tumoural cells besides the central nervous system. We hypothesized that 3 non-synonymous *LEPR* polymorphisms (Gln223Arg, Lys656Asn and Lys109Arg) may be associated with prostate cancer (PCa) risk and aggressiveness.
Methods: This case-control study was conducted in histologically confirmed PCa (n = 1382) and benign disease patients (n = 471). We used Real-Time PCR and PCR-RFLP in order to investigate genotype distributions of the LEPR polymorphisms in these populations.
Results: Age- and BMI-adjusted binary logistic regression showed decreased PCa risk for LEPR Gln223Arg Arg carriers (aOR = 0.56; 95% CI = 0.38–0.83; $P = 0.003$). Cumulatively, we observed an association between *LEPR* Lys656Asn Asn carriers with higher Gleason score ($P = 0.008$). In PCa patients, multivariate Cox regression analysis evidenced that LEPR Lys109Arg Lys carriers had lower time-to-bone metastasis (HR = 0.37; 95% CI = 0.14–0.95; P = 0.039), after adjustment for Gleason score, stage of disease and PSA level.
Conclusions: Results from this large study using biopsy-proven absence of PCa in the control group, suggest that the non-synonymous polymorphism LEPR Gln223Arg is associated with PCa development and may be a potential molecular marker of susceptibility. Conversely, the polymorphism LEPR Lys109Arg might be linked with bone metastasis mechanisms, influencing the