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Genetic variants in *5-HTTLPR*, *BDNF*, *HTR1A*, *COMT*, and *FKBP5* and risk for treated depression after cancer diagnosis

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Abstract

Background—The role of gene–environment interactions in the pathogenesis of depression is unclear. Previous studies addressed vulnerability for depression after childhood adversity and stressful life events among carriers of numerous specific genetic variants; however, the importance of individual genetic variants, the environmental exposures with which they interact, and the magnitude of the risk conveyed by these interactions remain elusive.

Methods—We included 7,320 people with a first primary cancer identified in the prospective Diet, Cancer and Health study in an exposed-only cohort study. The mean age of the individuals was 68 years (5th, 95th percentiles: 58, 78) at cancer diagnosis. Using Cox regression models and cumulative incidence plots, we analyzed the associations between genetic variants in *5-HTTLPR*, *BDNF*, *HTR1A*, *COMT*, and *FKBP5* and use of antidepressants as well as hospital contact for depression after diagnosis of cancer.

Results—Overall, we observed no statistically significant associations, with nonsignificant hazard ratio estimates for use of antidepressants of 0.95–1.07.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Conclusions—This study of elderly people indicates that it is unlikely that the investigated genetic variants are clinically relevantly associated with depression after diagnosis of cancer. The mechanisms for gene–environment interactions in younger individuals are probably different, and we advise caution in extrapolating our results to early life stress. However, conclusion from the present study might be generalizable to elderly persons exposed to other stressful life events.

Keywords

cancer; candidate genes; depression; gene–environment interaction; stressful life events

1 INTRODUCTION

Gene–environment interactions hypothesized to affect risk for depression have been investigated in numerous studies during the past 15 years. However, few certainties and clinically relevant insights have been achieved and the field is characterized by controversy (Munafò, 2015; Rutter, Thapar, and Pickles, 2009; Taylor et al., 2016; Zammit, Owen, & Lewis, 2010) with a continued need for improving our understanding of the role of gene–environment interactions in the development of depression (Dunn et al., 2015; Krishnan et al., 2010; Uher, 2014). Meta-analytic reviews have addressed the need for greater attention to the type of exposures as well as age at exposure. Thus, the most recent meta-analysis of serotonin transporter linked polymorphic region (*5-HTTLPR*), stressful life events and depression report evidence for the existence of a gene–environment interaction; however, as the authors pointed out, many well-conducted studies did not observe the interaction (Sharpley, Palanisamy, Glyde, Dillingham, & Agnew, 2014). In addition, a meta-analysis of the involvement of rs6265 in the brain-derived neurotropic factor (*BDNF*) gene in gene–environment interaction for depression found more evidence for this genetic variant having an effect on risk for depression in relation to adult stressful life events than in relation to childhood adversities (Hosang, Shiles, Tansey, McGuffin, & Uher, 2014). Such observations combined with the general knowledge of the complexity of brain maturation and changes in gene expression across the life course (Gogtay et al., 2004; Kang et al., 2011; Nord, Pattabiraman, Visel, & Rubenstein, 2015) suggest that it is essential to investigate gene–environment interactions in specific contexts defined by the type of environmental exposure, the timing of exposures during course of life, and the genetic variants with which they might interact. Associated with increased prevalence of depression (Massie, 2004; Mitchell et al., 2011; van't Spijker, Trijsburg, & Duivenvoorden, 1997), posing a high risk of dying, often involving major surgery and adjuvant treatment with burdensome side effects, and having onset predominantly in late adulthood, we consider cancer to represent a homogenous life event.

Addressing methodological limitations of previous studies, including low statistical power and nonobjective assessment of stressful events, here we present an exposed-only study evaluating if six of the most investigated genetic variants were associated with pharmacologically as well as hospital-treated depression in a large, elderly population of cancer patients. The genetic variants investigated were the *5-HTTLPR* including the rs25531, the rs6562 in the *BDNF* gene, the rs6295 in the serotonin-receptor 1A (*HTR1A*)

gene, the rs4680 in the catechol-*O*-methyl transferase (*COMT*) gene, and the rs1360780 in the FK506-binding protein 5 (*FKBP5*) gene.

2 MATERIALS AND METHODS

2.1 Study population

The sample for this study was obtained from the Danish prospective cohort study: Diet, Cancer and Health (Tjonneland et al., 2007). Briefly, between December 1993 and May 1997, all 160,725 people aged 50–64 who were born in Denmark, who had never had a diagnosis of cancer and who lived in selected municipalities in or near Aarhus and Copenhagen, the two major cities of Denmark, were invited to participate. Fifty seven thousand fifty three participants were included and provided various biological materials, including blood samples, from which samples of purified DNA were stored.

For the current study, we identified all 7,641 participants with a first primary cancer diagnosed in 1998–2013 in the colon or rectum, pancreas, lung, breast, prostate, corpus uteri, ovaries, or urinary bladder, constituting 71% of all cancers diagnosed among Diet, Cancer and Health study participants in the period. We excluded 248 participants with previous hospital contacts for organic mental disorder, mental or behavioral disorder due to use of a psychoactive substance, schizophrenia, schizotypal, or delusional disorder or manic or bipolar episodes (ICD-8: 290–295.99, 296.19, 296.39, 303.00–304.99 and ICD-10: F00–F31). We also excluded 14 persons not residing in Denmark at diagnosis of cancer, 11 persons with cancer diagnosed simultaneously at two different sites, nine patients with male breast cancer and one person whose date of death was registered before diagnosis of cancer. We were unable to retrieve stored DNA samples from 38 people, leaving a final study population of 7,320. The selection of the study population is illustrated in Supporting Information Figure S1. We previously reported an investigation of associations between biallelic and triallelic variants of *5-HTTLPR* and use of antidepressants for a subset of the current study population, consisting of 806 people with colorectal cancer diagnosed in 1998–2009 (Suppli et al., 2015).

2.2 Data sources

We ensured accurate linkage of our study population with nationwide registries by using the unique personal identification number assigned to all Danish residents since 1968 (Pedersen, 2011). We obtained the date of diagnosis and type of cancer from the Danish Cancer Registry, which since 1943 has registered cancers diagnosed in Denmark with a high degree of completeness (Gjerstorff, 2011; Storm, Michelsen, Clemmensen, & Pihl, 1997). Diagnoses related to all inpatient contacts with Danish psychiatric hospitals have been registered in the Danish Psychiatric Central Research Register since 1969; outpatient contacts have been registered since 1995 (Mors, Perto, & Mortensen, 2011). From this register, we obtained the dates of diagnosis of organic mental disorder, mental or behavioral disorder due to use of a psychoactive substance, schizophrenia, schizotypal or delusional disorder, manic or bipolar episodes, and depressive episodes (International Classification of Disease revision 8 (ICD-8): 290–295.99, 296.09–296.39, 303.00– 304.99 and ICD-10: F00–F33), representing severe mental disorders. In Denmark, antidepressants are available on

prescription only, and, since January 1, 1995, all prescription drugs dispensed at Danish pharmacies have been recorded in the Danish National Prescription Registry (Kildemoes, Sørensen, & Hallas, 2011). To measure depression diagnosed and treated pharmacologically by a physician, we retrieved information on all antidepressants (Anatomical Therapeutic Chemical classification (ATC): N06A) dispensed in 1995–2013. Dates of death and migration were obtained from the Danish Civil Registration System (Pedersen, 2011), the highest educational level attained by 30 September in the year preceding that of cancer diagnosis from Danish education registers (Jensen et al., 2011) and cohabitation status (Statistics Denmark, 2016) on 1 January of the year of cancer diagnosis from Statistics Denmark. The Danish National Patient Registry has registered all inpatient hospital contacts for somatic diseases since 1977 and all outpatients hospital contacts since 1995 (Lynge, Sandegaard, & Rebolj, 2011). From the discharge diagnoses, we calculated individual Charlson Comorbidity Index scores at the date of cancer diagnosis. The original index includes 19 diseases assigning each a weighted score representing the 1-year relative risk of dying. We used a modified version not including the index cancer (Charlson, Pompei, Ales, & MacKenzie, 1987; Dalton et al., 2008).

2.3 DNA analyses

Four functional single nucleotide polymorphisms (SNPs) in genes encoding the brain derived neurotrophic factor (*BDNF*; rs6265) (Chen et al., 2004; Egan et al., 2003), serotonin receptor 1A (*HTR1A*; rs6295) (Lemonde et al., 2003), catechol-*O*-methyl transferase (*COMT*; rs4680)(Lachman et al., 1996), and the FK506-binding protein 5 gene (*FKBP5;* rs1360780)(Binder et al., 2004) were determined by KASP genotyping with individual genotypes interpreted automatically by relevant software.

Variants in the serotonin transporter linked polymorphic region (*5-HTTLPR*) were determined by DNA sequencing. We determined the zygosity of long (L) and short (S) alleles visually. For all long alleles, we determined whether an adenine (A) or a guanine (G) was present at the rs25531 locus. Thus, we were able to distinguish biallelic (LL, LS, SS) and triallelic (high: L_AL_A; intermediate: L_AL_G, SL_A; low: L_GL_G, SL_G, SS) genotypes according to the transcriptional activity of *5-HTTLPR*.

The genotypes of *BDNF* rs6265 ($P = 0.79$), *HTR1A* rs6295 ($P = 1.00$), *COMT* rs4680 ($P = 0.79$), *FKBP5* rs1360780 ($P = 0.41$) and the biallelic *5-HTTLPR* ($P = 0.79$) were all in Hardy–Weinberg equilibrium. The triallelic *5-HTTLPR* genotype proportions (L_AL_A, $n = 1881$; L_AL_G, $n = 480$; SL_A, $n = 2962$; L_GL_G, $n = 58$; SL_G, $n = 394$; SS, $n = 1262$) were not in Hardy–Weinberg equilibrium ($P = 0.001$). However, the proportion of L_A (51%), L_G (7%), and S (42%) alleles were similar to the proportions found in a previous Danish study (Rasmussen, Bagger, Tanko, Christiansen, & Werge, 2009) and the distribution according to transcriptional activity (high: 27%, intermediate: 49%, low: 24%) resembles previous observations in Northern European populations (Araya et al., 2009; Bukh et al., 2009; Reinelt et al., 2013).

2.4 Statistical methods

We determined the incidence density rates for use of antidepressants in our study population in the years around the cancer diagnosis with follow-up from 3 years before cancer diagnosis until first prescription of antidepressants, emigration, diagnosis of a second cancer, hospital contact with a diagnosis of severe mental disorder, death, or 5 years after cancer diagnosis, whichever came first.

We assessed differences in sex, age at diagnosis of cancer, sociodemographic characteristics, treatment for depression before cancer, calendar year of cancer diagnosis and type of cancer according to genotype with χ^2 tests for categorical variables, and analysis of variance for continuous variables.

In primary analyses, we used Cox regression analyses to determine associations between being a heterozygote or a homozygote for the hypothesized risk allele of each genetic variant and use of antidepressants after cancer diagnosis. Homozygotes for the hypothesized non-risk allele were used as the reference group. This strategy yielded 12 statistical tests, and we decided to apply Bonferroni correction to our analyses, with an α of 0.0042. With differences dependent on genotype distributions, this gave us power to detect hazard ratios (HRs) of approximately 1.25.

The secondary analyses included plots of the cumulative incidence of use of antidepressants according to genotype with diagnosis of a second cancer, a hospital contact for severe mental disorder and death as competing risks. Secondary Cox regression analyses were performed to determine associations between genotypes and hospital contacts for depression after diagnosis of cancer. Associations between genotypes and use of antidepressants were analyzed according to time since cancer diagnosis (1–6 months, 7–12 months, 2 years, 3 years, 4–5 years, and 6–8 years). We also determined associations between genotypes and use of antidepressants in models according to sex, cancer prognosis (5-year survival > 80%: prostate, breast, and corpus uteri cancer; 5-year survival 40–70%: ovary, bladder, and colorectal cancer; 5-year survival < 20%: lung and pancreas cancer) and the four major cancer types (prostate, breast, colorectal, and lung). To determine whether the hypothesized associations were more pronounced for incident depression, we conducted separate Cox analyses for participants with and without hospital contact for depression (ICD-8: 296.09 and 296.29; ICD-10:F32–33) between 1969 and diagnosis of cancer and/or use of antidepressants during the 3 years preceding diagnosis of cancer.

After assessing the assumption of proportionality in all Cox models, we included sex and calendar year of cancer diagnosis (continuous variable) as covariates and stratified on age at cancer diagnosis (<60, 60–64, 65–69, 70–74, ≥75 years). In analyses of cumulative incidence of use of antidepressants, we included sex as a covariate and tested differences between genotypes with Gray's test. In Cox models and for cumulative incidence plots, time since diagnosis of cancer was used as the underlying time, and participants were followed until outcome or any of the following censoring events: migration, diagnosis of a second cancer, hospital contact with a diagnosis of severe mental disorder (not including depression), death or 31 December 2013, whichever came first.

We performed χ^2 tests, analysis of variance, and Cox regression analysis with the FREQ, UNIVARIATE, and PHREG procedures in SAS version 9.3. Cumulative incidence was analyzed with the "cmprsk" package in R version 3.1.2 (Gray, 2014; R Core Team, 2013).

2.5 Ethical considerations

This study was approved by the Committee on Health Research Ethics, Capital Region of Denmark (protocol number H-15005195).

3 RESULTS

In our study population, incident use of antidepressants increased from 30 new users per 1,000 person-years in the year preceding cancer diagnosis to 87 new users per 1,000 person-years in the year after cancer diagnosis (Fig. 1).

In general, baseline characteristics and cancer type were not associated with the genetic variants (Table 1); however, the comorbidity score was significantly associated with *FKBP5* ($P = 0.03$).

In the primary analyses, all HR estimates were 0.95–1.07, and none of the genetic variants was statistically significantly associated with risk for use of antidepressants after cancer (Table 2). Inclusion of the comorbidity score in the analysis of the *FKBP5* did not affect the estimate (results not shown). Further, we found no statistically significant associations between the genetic variants and hospital contact for depression as the first event after cancer (Table 2). Cumulative incidence plots showed no statistically significant associations between the investigated genotypes and the probability of use of antidepressants (Fig. 2). Our Cox analysis of hazard for use of antidepressants according to time since cancer diagnosis revealed no statistically significant results and gave no indication that genetic variants are more likely to be associated with the outcome in periods closer to the diagnosis (Supporting Information Table S1).

Cox regression analyses by sex, 5-year cancer prognosis (>80%, 40–70%, <20%) and cancer type are shown in Figure 3. The HRs for use of antidepressants were 0.83–1.31, except for statistically non-significantly higher estimates for the AA genotype of the *BDNF* rs6265 among people with poor-prognosis cancers (HR, 1.76; 99.58% CI, 0.94–3.30), specifically for lung cancer (HR 1.60; 99.58% CI, 0.76–3.38). However, these estimates were based on only 72 participants with poor-prognosis cancer and the rare AA genotype, of whom 23 were treated with antidepressants.

Cox analyses separated according to treatment for depression before cancer diagnosis showed similar nonsignificant associations of genotypes with antidepressant use after cancer between groups of people not treated and treated for depression before cancer, respectively (Supporting Information Table S2).

4 DISCUSSION

This large study of hypothesized interactions between genetic variants in *5-HTTLPR*, *BDNF*, *HTR1A*, *COMT*, and *FKBP* and stressful life events and the risk for depression

indicates that it is unlikely that any of these genetic variants has a clinically relevant individual effect on risk for depression in elderly people diagnosed with cancer.

Previous meta-analyses of the *5-HTTLPR* indicated that the hypothesized gene–environment interaction was clearer in studies with objective measurement of stress or medical conditions as stressors (Karg, Burmeister, Shedden, & Sen, 2011; Sharpley et al., 2014); however, in the present study of the objectively assessed medical condition of cancer diagnosis, we observed no such interaction. One meta-analysis of the *BNDF* rs6265, found stronger evidence of an interaction with stressful life events in adults than in children (Hosang et al., 2014). Our study does not support this hypothesis in older adults. Previous reports of significant associations between the investigated genetic variants in *HTR1A*, *COMT*, and *FKBP5*, adverse environmental exposure and risk for depression relied on few patients with depression who had the investigated genotype and who were also exposed to stress adverse environmental exposure and risk for depression relied on few patients with depression who had the investigated genotype and who were also exposed to stress (Galvão-de Almeida et al., 2014; Kraus et al., 2007; Lebe et al., 2013; Comasco et al., 2011; Doornbos et al., 2009; Mandelli et al., 2007; Appel et al., 2011; Kang et al., 2012; Lahti et al., 2015; Nyman et al., 2011; Scheuer et al., 2016; Shinozaki et al., 2011; Zimmermann et al., 2011). Our study, with a large number of cases, does not support an omnipresent existence of interactions between these genetic variants and adverse environmental exposures on risk for depression.

Our population was similar in size to the total number of people evaluated for objectively measured stressful events or medical conditions in the most recent, largest meta-analysis of *5-HTTLPR* (Sharpley et al., 2014) and corresponds to the total number of people in studies of the interaction between adult stressful life events and *BDNF* rs6265 polymorphism in another meta-analysis (Hosang et al., 2014). In addition, with this study, we approximately doubled the total number of people investigated for interactions between each of the selected genetic variants in *COMT*, *HTR1A* and *FKBP5* and adverse environmental exposures on risk for depression.

Our study overcame several fundamental challenges in studying gene–environment interactions (Thomas, 2010). First, we identified cancer diagnoses in a nationwide, virtually complete register and thus accurately ascertained the occurrence and timing of a severely stressful life event with no recall bias. As a cancer diagnosis implies an increased risk for death and also often involves intense, severe treatment with serious acute, enduring side effects, we consider that it is a stressful life event with an objective negative impact and long-term contextual threat, as proposed by Paykel (1983), Brown and Harris (1978) and more recently Kendler, Karkowski, and Prescott (1998). Accordingly, and in line with previous reports (Massie, 2004; Mitchell et al., 2011; van't Spijker et al., 1997), we observed increased use of antidepressants after diagnosis of cancer in this study. Second, we used antidepressant use as the observer-based measure of depression recognized and pharmacologically treated by a physician as well as hospital contacts for depression as a measure of the most severe depression, which allowed longitudinal assessment of depression and investigation of hypothesized interactions with survival analyses and competing risk analyses. Third, by applying an exposed-only design, we focused on people in whom the effect of the investigated genetic variants on risk for depression is hypothesized to be

present, maximizing statistical power. Thus, a unique feature of the present study is that the results are based on hundreds of events in strata of genotype by stress exposure. Further, the exposed-only design allowed us to sidestep controversial issues involved in distinguishing biological versus statistical interaction as well as additive versus multiplicative interactions (Karg et al., 2012; Kendler et al., 2010; Moffitt, Caspi, and Rutter, 2006; Rutter et al., 2009). Fourth, our population was ethnically homogeneous, reducing the risk for bias due to population stratification. However, a limitation of our study population is that participants in the Diet, Cancer and Health study were generally socioeconomically privileged (Larsen et al., 2012) and probably had higher health literacy. Thus, our results might not be generalizable to populations that are less health literate.

Further limitations of our study include the fact that use of antidepressants as a measure of pharmacologically treated depression introduces some misclassification, as all cases of depression are not diagnosed and pharmacologically treated; for those that are treated, the median lag between onset of depression and diagnosis and possible treatment initiation is about 1 year (Wang et al., 2007). Further, although depression is the indication for about 75% of all prescribed antidepressants, these drugs are also prescribed for other indications, primarily anxiety and pain (Charles, Britt, Fahridin, & Miller, 2007; Loosbrock, Tomlin, Robinson, Obenchain, & Croghan, 2002; Trifiro et al., 2013). Nevertheless, we consider that any misclassification introduced by use of antidepressants as our primary outcome measure would be nondifferential and was unlikely to result in failure to observe any clinically relevant, true association between the investigated genetic variants and risk for depression. In addition, the secondary analyses of hospital contacts for depression—a valid measure of the most severe depression (Bock, Bukh, Vinberg, Gether, & Kessing, 2009)—did not confirm the hypothesized associations.

Some limitations also apply to use of a cancer diagnosis as a stressful life event. Thus, although we assumed that this was a stressful event for all the people included in this study, we did not assess the level of stress individually. Further, we used diagnosis of cancer as the baseline in our analysis, whereas physical symptoms and worry are probably present in the months preceding this date. Addition of an instrument such as the Interview for Recent Life Events, in which the time of occurrence, the independence of the depressive state, and the negative impact of the event are rated by an interviewer, might have clarified the individual level of stress posed by a diagnosis of cancer (Bukh et al., 2009; Paykel, 1997). A central concern in studies of the association between stressful life events and risk for depression, including studies of gene– environment interactions, is whether people prone to depression are more likely to expose themselves to the studied life events (Kendler, Karkowski, & Prescott, 1999). We showed previously that, although depression is generally not associated with an increased risk for cancer, people with depression are at increased risk for tobacco-related cancers (cancers of the urinary bladder, lung, and pancreas) (Dalton, Mellemkjær, Olsen, Mortensen, & Johansen, 2002). In our study, 72% of the population had nontobacco-related cancers (prostate, breast, corpus uteri, ovarian, and colorectal cancers), and analyses separated by cancer type did not indicate different associations between cancer types. Furthermore, the genotype distribution was identical for all cancer types.

The triallelic *5-HTTLPR* genotype was not in Hardy–Weinberg equilibrium, indicating that our DNA analysis of this genetic variant was imperfect. As the disequilibrium was primarily the consequence of a higher than expected number of participants with the rare L_GL_G genotype we reassessed the sequencing data for people with this genotype without finding reason to question the original calls. Thus, we consider it a minor limitation of our study that the triallelic *5-HTTLPR* genotype was not in Hardy–Weinberg equilibrium.

The similarity of the inflammatory processes observed in both tumor growth and depression (Sotelo, Musselman, & Nemeroff, 2014) possibly limits the generalizability of our results. Some of the increased incidence of depression after a diagnosis of cancer might be directly linked to inflammatory processes related to tumorigenesis, thus bypassing the higher order brain functions hypothesized to transduce psychosocial stress into depressive episodes (Slavich et al., 2014). In addition, our results are not necessarily generalizable to adversity in childhood or stressful life events in early adulthood. It is plausible that the biological mechanisms—including gene–environment interactions—involved in the increased risk for and poorer prognosis of adult depression associated with childhood adversity are specific to the sensitive periods of the maturing brain in early life (Andersen et al., 2008; Brown et al., 2008; Heim et al., 2012). Accordingly, Brown and Harris hypothesized that an effect of the *5-HTTLPR* on risk for depression after adult stressful life events would be present only among individuals exposed to childhood maltreatment (Brown et al., 2008). This hypothesis could account for the lack of positive findings for the other genetic variants included in this study, as well. A previous study found that *5-HTTLPR* interacted with childhood maltreatment specifically on the risk for persistent depression but not for single-episode depression in young adults (Uher et al., 2011), indicating that gene–environment interactions can affect only certain types or severity of depression. In the present study, neither analyses by treatment for depression before cancer nor analyses with hospital contacts for depression as a proxy measures for more severe depression indicated such differences.

Finally, as outlined by Keller, a number of statistical concerns have caused skepticism about the validity of previous positive findings of gene–environment interaction (Keller, 2014). Accordingly, it is possible that our presently reported negative findings are simply due to a nonexistence of the originally hypothesized involvement of the selected genetic variants in gene–environment interaction for depression.

5 CONCLUSION

We find it unlikely that any of the genetic variants we investigated have clinically relevant individual effects on the risk for depression after a diagnosis of cancer, and our results do not support hypotheses that these genetic variants interact with stressful life events to cause depression in elderly people.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Andersen SL, Teicher MH. Stress, sensitive periods and maturational events in adolescent depression. Trends in Neurosciences. 2008; 31(4):183–191. Retrieved from https://doi.org/10.1016/j.tins.2008.01.004. [PubMed: 18329735]

Appel K, Schwahn C, Mahler J, Schulz A, Spitzer C, Fenske K, Grabe HJ. Moderation of adult depression by a polymorphism in the FKBP5 gene and childhood physical abuse in the general population. Neuropsychopharmacology. 2011; 36(10):1982–1991. Retrieved from https://doi.org/10.1038/npp.2011.81. [PubMed: 21654733]

Araya R, Hu X, Heron J, Enoch MA, Evans J, Lewis G, Gold-man D. Effects of stressful life events, maternal depression and 5-HTTLPR genotype on emotional symptoms in pre-adolescent children. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2009; 150B(5):670–682. Retrieved from https://doi.org/10.1002/ajmg.b.30888.

Binder EB, Salyakina D, Lichtner P, Wochnik GM, Ising M, Pütz B, Deiml T. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Nature Genetics. 2004; 36(12):1319–1325. Retrieved from https://doi.org/10.1038/ng1479. [PubMed: 15565110]

Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV. Validity of the diagnosis of a single depressive episode in a case register. Clinical Practice and Epidemiology in Mental Health. 2009; 5:4. Retrieved from https://doi.org/10.1186/1745-0179-5-4. [PubMed: 19216741]

Brown GW, Harris T. Social origins of depression: A reply. Psychological Medicine. 1978; 8(04):577–588. Retrieved from https://doi.org/10.1017/S0033291700018791. [PubMed: 724871]

Brown GW, Harris TO. Depression and the serotonin transporter 5-HTTLPR polymorphism: A review and a hypothesis concerning gene–environment interaction. Journal of Affective Disorders. 2008; 111(1):1–12. Retrieved from https://doi.org/10.1016/j.jad.2008.04.009. [PubMed: 18534686]

Bukh JD, Bock C, Vinberg M, Werge T, Gether U, Vedel Kessing L. Interaction between genetic polymorphisms and stressful life events in first episode depression. Journal of Affective Disorders. 2009; 119(1–3):107–115. Retrieved from https://doi.org/10.1016/j.jad.2009.02.023. [PubMed: 19339052]

Charles J, Britt H, Fahridin S, Miller G. Mental health in general practice. Australian Family Physician. 2007; 36(4):200–201. [PubMed: 17392929]

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases. 1987; 40(5):373–383. [PubMed: 3558716]

Chen ZY, Patel PD, Sant G, Meng CX, Teng KK, Hempstead BL, Lee FS. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. Journal of Neuroscience. 2004; 24(18):4401–4411. Retrieved from https://doi.org/10.1523/JNEUROSCI.0348-04.2004. [PubMed: 15128854]

Comasco EA, Sylven SMB, Papadopoulos FCC, Sundstrom-Poromaa IB, Oreland LA, Skalkidou AB. Postpartum depression symptoms: A case-control study on monoaminergic functional polymorphisms and environmental stressors. Psychiatric Genetics. 2011; 21(1):19–28. Retrieved from https://doi.org/10.1097/YPG.0b013e328341a3c1. [PubMed: 21099450]

Dalton SO, Mellemkjær L, Olsen JH, Mortensen PB, Johansen C. Depression and cancer risk: A register-based study of patients hospitalized with affective disorders, Denmark, 1969–1993.

American Journal of Epidemiology. 2002; 155(12):1088–1095. Retrieved from https://doi.org/10.1093/aje/155.12.1088. [PubMed: 12048222]

Dalton SO, Steding-Jessen M, Gislum M, Frederiksen K, Engholm G, Schuz J. Social inequality and incidence of and survival from cancer in a population-based study in Denmark, 1994–2003: Background, aims, material and methods. European Journal of Cancer. 2008; 44(12):1938–1949. [PubMed: 18684615]

Denmark Statistics. Documentation of high quality variables, family type. 2016. Retrieved from http://www.dst.dk/da/TilSalg/Forskningsservice/Dokumentation/hoejkvalitetsvariable/familier/familie-type

Doornbos B, Dijck-Brouwer DAJ, Kema IP, Tanke MAC, van Goor SA, Muskiet FAJ, Korf J. The development of peripartum depressive symptoms is associated with gene polymorphisms of MAOA, 5-HTT and COMT. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2009; 33(7):1250–1254. Retrieved from https://doi.org/10.1016/j.pnpbp.2009.07.013. [PubMed: 19625011]

Dunn EC, Brown RC, Dai Y, Rosand J, Nugent NR, Amstadter AB, Smoller JW. Genetic determinants of depression: Recent findings and future directions. Harvard Review of Psychiatry. 2015; 23(1): 1–18. Retrieved from https://doi.org/10.1097/HRP.0000000000000054. [PubMed: 25563565]

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Weinberger DR. The BDNF val66met polymor phism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003; 112(2):257–269. [PubMed: 12553913]

Galvão-de Almeida A, Quarantini LC, Tartaglioni AG, Lyra AC, Parise CL, Paraná R, Guindalini C. Serotonin-1A receptor CC genotype is associated with persistent depression related to interferon-alpha in hepatitis C patients. General Hospital Psychiatry. 2014; 36(3):255–260. Retrieved from https://doi.org/10.1016/j.genhosppsych.2013.12.007. [PubMed: 24462335]

Gjerstorff ML. The Danish cancer registry. Scandinavian Journal of Public Health. 2011; 39(7 Suppl): 42–45. Retrieved from https://doi.org/10.1177/1403494810393562. [PubMed: 21775350]

Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Thompson PM. Dynamic mapping of human cortical development during childhood through early adulthood. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101(21):8174–8179. Retrieved from https://doi.org/10.1073/pnas.0402680101. [PubMed: 15148381]

Gray B. Cmprsk: Subdistribution analysis of competing risks. R package version. 2014; 2:2–7. Retrieved from https://CRAN.R-project.org/package=cmprsk.

Heim C, Binder EB. Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene–environment interactions, and epigenetics. Experimental Neurology. 2012; 233(1):102–111. Retrieved from https://doi.org/10.1016/j.expneurol.2011.10.032. [PubMed: 22101006]

Hosang GM, Shiles C, Tansey KE, McGuffin P, Uher R. Interaction between stress and the BDNF Val66Met polymorphism in depression: A systematic review and meta-analysis. BMC Medicine. 2014; 12:7. Retrieved from https://doi.org/10.1186/1741-7015-12-7. [PubMed: 24433458]

Jensen VM, Rasmussen AW. Danish education registers. Scandinavian Journal of Public Health. 2011; 39(7 Suppl):91–94. Retrieved from https://doi.org/10.1177/1403494810394715. [PubMed: 21775362]

Kang HJ, Kawasawa YI, Cheng F, Zhu Y, Xu X, Li M, Weinberger DR. Spatio-temporal transcriptome of the human brain. Nature. 2011; 478(7370):483–489. Retrieved from https://doi.org/10.1038/nature10523. [PubMed: 22031440]

Kang JI, Chung HC, Jeung HC, Kim SJ, An SK, Namkoong K. FKBP5 polymorphisms as vulnerability to anxiety and depression in patients with advanced gastric cancer: A controlled and prospective study. Psychoneuroendocrinology. 2012; 37(9):1569–1576. Retrieved from https://doi.org/10.1016/j.psyneuen.2012.02.017. [PubMed: 22459275]

Karg K, Burmeister M, Shedden K, Sen S. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation. Archives of General Psychiatry. 2011; 68(5):444–454. Retrieved from https://doi.org/10.1001/archgenpsychiatry.2010.189. [PubMed: 21199959]

Karg K, Sen S. Gene × Environment interaction models in psychiatric genetics. Current Topics in Behavioral Neurosciences. 2012; 12:441–462. Retrieved from https://doi.org/10.1007/7854_2011_184. [PubMed: 22241248]

Keller MC. Gene-by-environment interaction studies have not properly controlled for potential confounders: The problem and the (simple) solution. Biological Psychiatry. 2014; 75(1):18–24. Retrieved from https://doi.org/10.1016/j.biopsych.2013.09.006. [PubMed: 24135711]

Kendler KS, Gardner CO. Interpretation of interactions: Guide for the perplexed. British Journal of Psychiatry. 2010; 197(3):170–171. Retrieved from https://doi.org/10.1192/bjp.bp.110.081331. [PubMed: 20807958]

Kendler KS, Karkowski LM, Prescott CA. Stressful life events and major depression: Risk period, long-term contextual threat, and diagnostic specificity. Journal of Nervous and Mental Disease. 1998; 186(11):661–669. [PubMed: 9824167]

Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. American Journal of Psychiatry. 1999; 156(6):837–841. [PubMed: 10360120]

Kildemoes HW, Sørensen HT, Hallas J. The Danish national prescription registry. Scandinavian Journal of Public Health. 2011; 39(7 suppl):38–41. Retrieved from https://doi.org/10.1177/1403494810394717. [PubMed: 21775349]

Kraus MR, Al-Taie O, Schäfer A, Pfersdorff M, Lesch KP, Scheurlen M. Serotonin-1A receptor gene HTR1A variation predicts interferon-induced depression in chronic hepatitis C. Gastroenterology. 2007; 132(4):1279–1286. Retrieved from https://doi.org/10.1053/j.gastro.2007.02.053. [PubMed: 17408646]

Krishnan V, Nestler EJ. Linking molecules to mood: New insight into the biology of depression. American Journal of Psychiatry. 2010; 167(11):1305–1320. Retrieved from https://doi.org/10.1176/appi.ajp.2009.10030434. [PubMed: 20843874]

Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM. Human catechol-*O*-methyltransferase pharmacogenetics: Description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics. 1996; 6(3):243–250. [PubMed: 8807664]

Lahti J, Ala-Mikkula H, Kajantie E, Haljas K, Eriksson JG, Räikkönen K. Associations between self-reported and objectively recorded early life stress, FKBP5 polymorphisms, and depressive symptoms in midlife. Biological Psychiatry. 2015; 80(11):869–877. Retrieved from https://doi.org/10.1016/j.biopsych.2015.10.022. [PubMed: 26740367]

Larsen SB, Dalton SO, Schüz J, Christensen J, Overvad K, Tjønneland A, Olsen A. Mortality among participants and nonparticipants in a prospective cohort study. European Journal of Epidemiology. 2012; 27(11):837–845. [PubMed: 23070658]

Lebe M, Hasenbring MI, Schmieder K, Jetschke K, Harders A, Epplen JT, Kötting J. Association of serotonin-1A and -2A receptor promoter polymorphisms with depressive symptoms, functional recovery, and pain in patients 6 months after lumbar disc surgery. Pain. 2013; 154(3):377–384. Retrieved from https://doi.org/10.1016/j.pain.2012.11.017. [PubMed: 23318131]

Lemonde S, Turecki G, Bakish D, Du L, Hrdina PD, Bown CD, Albert PR. Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. Journal of Neuroscience. 2003; 23(25):8788–8799. [PubMed: 14507979]

Loosbrock DL, Tomlin ME, Robinson RL, Obenchain RL, Croghan TW. Appropriateness of prescribing practices for serotonergic antidepressants. Psychiatric Services. 2002; 53(2):179–184. [PubMed: 11821548]

Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. Scandinavian Journal of Public Health. 2011; 39(7 Suppl):30–33. Retrieved from https://doi.org/10.1177/1403494811401482. [PubMed: 21775347]

Mandelli L, Serretti A, Marino E, Pirovano A, Calati R, Colombo C. Interaction between serotonin transporter gene, catechol-*O*-methyltransferase gene and stressful life events in mood disorders. International Journal of Neuropsychopharmacology. 2007; 10(4):437–447. Retrieved from https://doi.org/10.1017/S1461145706006882. [PubMed: 16756688]

Massie MJ. Prevalence of depression in patients with cancer. Journal of the National Cancer Institute Monographs. 2004; 32:57–71.

Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, Meader N. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: A meta-analysis of 94 interview-based studies. Lancet Oncology. 2011; 12(2):160–174. Retrieved from https://doi.org/10.1016/S1470-2045(11)70002-X. [PubMed: 21251875]

Moffitt TE, Caspi A, Rutter M. Measured gene–environment interactions in psychopathology. Perspectives on Psychological Science. 2006; 1(1):5–27. [PubMed: 26151183]

Mors O, Perto GP, Mortensen PB. The Danish psychiatric central research register. Scandinavian Journal of Public Health. 2011; 39(7 Suppl):54–57. [PubMed: 21775352]

Munafò MR. Understanding the candidate gene × environment interaction debate: Epistemological or evidential divide? International Journal of Epidemiology. 2015; 44(4):1130–1132. Retrieved from https://doi.org/10.1093/ije/dyv056. [PubMed: 25855723]

Nord AS, Pattabiraman K, Visel A, Rubenstein JLR. Genomic perspectives of transcriptional regulation in forebrain development. Neuron. 2015; 85(1):27–47. Retrieved from https://doi.org/10.1016/j.neuron.2014.11.011. [PubMed: 25569346]

Nyman ES, Sulkava S, Soronen P, Miettunen J, Loukola A, Leppä V, Paunio T. Interaction of early environment, gender and genes of monoamine neurotransmission in the aetiology of depression in a large population-based Finnish birth cohort. BMJ Open. 2011; 1(1):e000087. Retrieved from https://doi.org/10.1136/bmjopen-2011-000087.

Paykel ES. Methodological aspects of life events research. Journal of Psychosomatic Research. 1983; 27(5):341–352. Retrieved from https://doi.org/10.1016/0022-3999(83)90065-X. [PubMed: 6668560]

Paykel ES. The interview for recent life events. Psychological Medicine. 1997; 27(02):301–310. Retrieved from https://doi.org/10.1017/S0033291796004424. [PubMed: 9089823]

Pedersen CB. The Danish civil registration system. Scandinavian Journal of Public Health. 2011; 39(7 Suppl):22–25. Retrieved from https://doi.org/10.1177/1403494810387965. [PubMed: 21775345]

Rasmussen H, Bagger Y, Tanko LB, Christiansen C, Werge T. Lack of association of the serotonin transporter gene promoter region polymorphism, 5-HTTLPR, including rs25531 with cigarette smoking and alcohol consumption. American Journal of Medical Genetics Part B, Neuropsychiatric Genetics. 2009; 150B(4):575–580. Retrieved from https://doi.org/10.1002/ajmg.b.30880.

Core Team R. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2013. Retrieved fromhttp://www.R-project.org/

Reinelt E, Stopsack M, Aldinger M, John U, Grabe HJ, Barnow S. Testing the diathesis-stress model: 5-HTTLPR, childhood emotional maltreatment, and vulnerability to social anxiety disorder. American Journal of Medical Genetics Part B, Neuropsychiatric Genetics. 2013; 162B(3):253–261. Retrieved from https://doi.org/10.1002/ajmg.b.32142.

Rutter M, Thapar A, Pickles A. Gene–environment interactions: Biologically valid pathway or artifact? Archives of General Psychiatry. 2009; 66(12):1287–1289. Retrieved from https://doi.org/10.1001/archgenpsychiatry.2009.167. [PubMed: 19996033]

Scheuer S, Ising M, Uhr M, Otto Y, von Klitzing K, Klein AM. FKBP5 polymorphisms moderate the influence of adverse life events on the risk of anxiety and depressive disorders in preschool children. Journal of Psychiatric Research. 2016; 72:30–36. Retrieved from https://doi.org/10.1016/j.jpsychires.2015.10.009. [PubMed: 26521051]

Sharpley CF, Palanisamy SKA, Glyde NS, Dillingham PW, Agnew LL. An update on the interaction between the serotonin transporter promoter variant (5-HTTLPR), stress and depression, plus an exploration of non-confirming findings. Behavioural Brain Research. 2014; 273:89–105. Retrieved from https://doi.org/10.1016/j.bbr.2014.07.030. [PubMed: 25078292]

Shinozaki G, Jowsey S, Amer HM, Biernacka J, Colby C, Walker D, Mrazek DA. Relationship between FKBP5 polymorphisms and depression symptoms among kidney transplant recipients. Depression and Anxiety. 2011; 28(12):1111–1118. Retrieved from https://doi.org/10.1002/da.20879. [PubMed: 22134958]

Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. Psychological Bulletin. 2014; 140(3):774–815. Retrieved from https://doi.org/10.1037/a0035302. [PubMed: 24417575]

Sotelo JL, Musselman D, Nemeroff C. The biology of depression in cancer and the relationship between depression and cancer progression. International Review of Psychiatry. 2014; 26(1):16–30. Retrieved from https://doi.org/10.3109/09540261.2013.875891. [PubMed: 24716498]

Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish cancer registry—History, content, quality and use. Danish Medical Bulletin. 1997; 44(5):535–539. [PubMed: 9408738]

Suppli NP, Bukh JD, Moffitt TE, Caspi A, Johansen C, Albieri V, Dalton SO. 5-HTTLPR and use of antidepressants after colorectal cancer including a meta-analysis of 5-HTTLPR and depression after cancer. Translational Psychiatry. 2015; 5(9):e631. Retrieved from https://doi.org/10.1038/tp.2015.121. [PubMed: 26327689]

Taylor AE, Munafò MR. Triangulating meta-analyses: The example of the serotonin transporter gene, stressful life events and major depression. BMC Psychology. 2016; 4(1):23. Retrieved from https://doi.org/10.1186/s40359-016-0129-0. [PubMed: 27240561]

Thomas D. Gene–environment-wide association studies: Emerging approaches. Nature Reviews Genetics. 2010; 11(4):259–272. Retrieved from https://doi.org/10.1038/nrg2764.

Tjonneland A, Olsen A, Boll K, Stripp C, Christensen J, Engholm G, Overvad K. Study design, exposure variables, and socioeconomic determinants of participation in diet, cancer and health: A population-based prospective cohort study of 57,053 men and women in Denmark. Scandinavian Journal of Public Health. 2007; 35(4):432–441. [PubMed: 17786808]

Trifiro G, Tillati S, Spina E, Ferrajolo C, Alacqua M, Aguglia E, Samani F. A nationwide prospective study on prescribing pattern of antidepressant drugs in Italian primary care. European Journal of Clinical Pharmacology. 2013; 69(2):227–236. Retrieved from https://doi.org/10.1007/s00228-012-1319-1. [PubMed: 22706616]

Uher R. Gene–environment interactions in common mental disorders: An update and strategy for a genome-wide search. Social Psychiatry and Psychiatric Epidemiology. 2014; 49(1):3–14. Retrieved from https://doi.org/10.1007/s00127-013-0801-0. [PubMed: 24323294]

Uher R, Caspi A, Houts R, Sugden K, Williams B, Poulton R, Moffitt TE. Serotonin transporter gene moderates childhood maltreatment's effects on persistent but not single-episode depression: Replications and implications for resolving inconsistent results. Journal of Affective Disorders. 2011; 135(1–3):56–65. Retrieved from https://doi.org/10.1016/j.jad.2011.03.010. [PubMed: 21439648]

van't Spijker A, Trijsburg RW, Duivenvoorden HJ. Psychological sequelae of cancer diagnosis: A meta-analytical review of 58 studies after 1980. Psychosomatic Medicine. 1997; 59(3):280–293. [PubMed: 9178339]

Wang PS, Angermeyer M, Borges G, Bruffaerts R, Tat CW, de GG, Ustun TB. Delay and failure in treatment seeking after first onset of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry. 2007; 6(3):177–185. [PubMed: 18188443]

Zammit S, Owen MJ, Lewis G. Misconceptions about gene– environment interactions in psychiatry. Evidence-Based Mental Health. 2010; 13(3):65–68. Retrieved from https://doi.org/10.1136/ebmh.13.3.65. [PubMed: 20682811]

Zimmermann P, Bruckl T, Nocon A, Pfister H, Binder EB, Uhr M, Ising M. Interaction of FKBP5 gene variants and adverse life events in predicting depression onset: Results from a 10-year prospective community study. American Journal of Psychiatry. 2011; 168(10):1107–1116. Retrieved from https://doi.org/10.1176/appi.ajp.2011.10111577. [PubMed: 21865530]

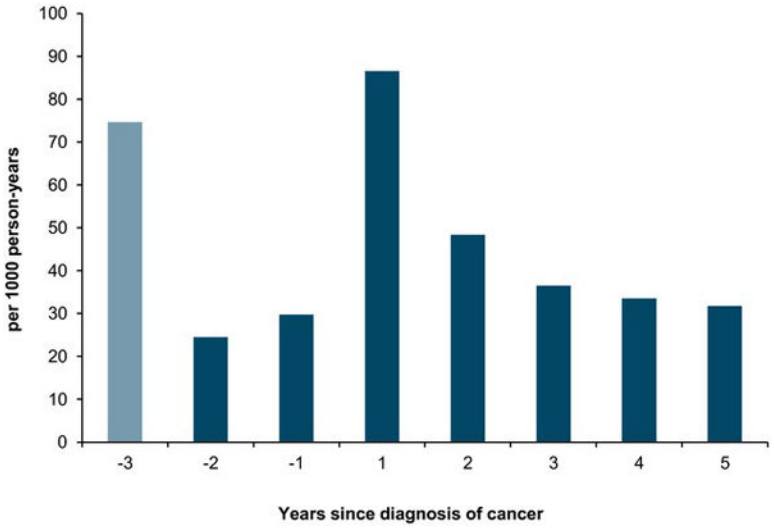

FIGURE 1.

Incident use of antidepressants 3 years before and 5 years after cancer diagnosis among 7,320 persons from the Diet, Cancer and Health cohort study with one of eight major cancer types diagnosed in 1998–2013. Year 3 (−3) before cancer diagnosis constitutes a “wash-in” period to identify both prevalent and incident users

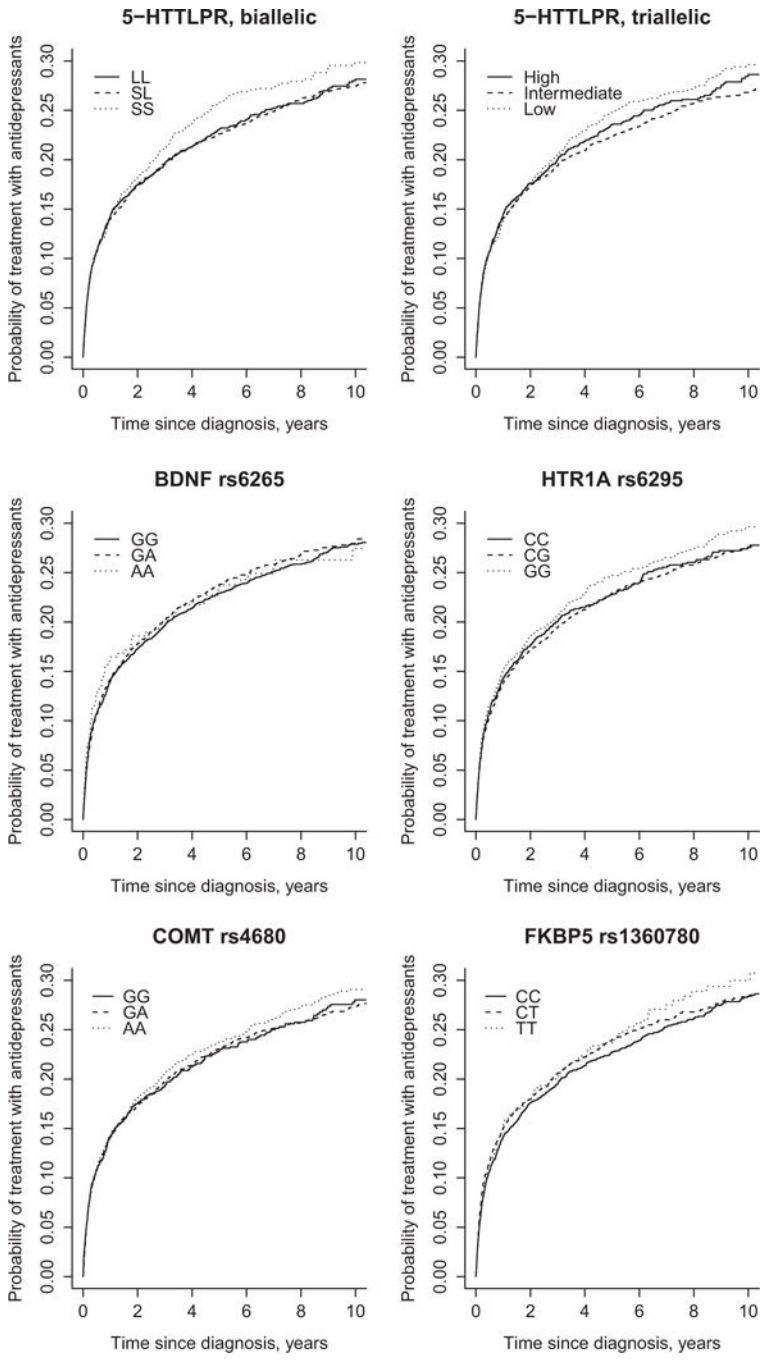

FIGURE 2.

Cumulative incidence plots of probability of use of antidepressants after cancer diagnosis according to genotype among 7,320 people in the Diet, Cancer and Health cohort study with one of eight major cancer types diagnosed in 1998–2013. Diagnosis of second cancer, hospital contact for severe mental disorder (ICD-10: F00–31) and death were included as competing events. Differences between genotypes were tested with Gray's test

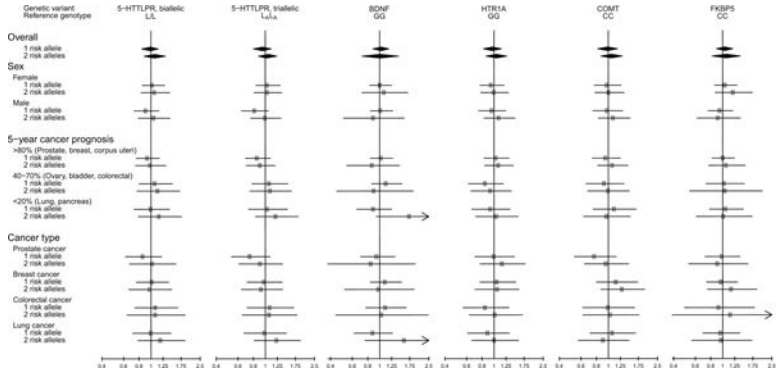

FIGURE 3.

Forest plot of hazard ratios and 99.58% confidence intervals for use of antidepressants after cancer diagnosis from overall Cox analyses and Cox analyses by sex, cancer prognosis according to 5-year survival and the four most common cancer types, among 7,320 people in the Diet, Cancer and Health cohort study with one of eight major cancer types diagnosed in 1998–2013. The overall estimates plotted with diamonds correspond to the hazard ratio estimates presented in Table 2. The *x*-axis of each plot is on a logarithmic scale. Hazard ratio estimates on the right side of the reference value of 1 indicate higher risk for use of antidepressants associated with hypothesized risk alleles

TABLE 1

Baseline characteristics of 7,320 people in the Diet, Cancer and Health cohort study with first primary cancer at one of eight major sites diagnosed in 1998–2013, including test for differences between genotypes within each tested genetic variant

			Test for differences in baseline characteristics (*P*)					
			5-HTTLPR genotypes					
	n	**(%)**	**Biallelic**	**Triallelic**	**BDNF**	**HTR1A**	**COMT**	**FKBP5**
Sex			0.86	0.99	0.90	0.77	0.29	0.64
Female	3,527	(48)						
Male	3,793	(52)						
Age at diagnosis (years)			0.20	0.16	0.90	0.38	0.25	0.80
<60	694	(9)						
60–64	1,411	(19)						
65–69	2,362	(32)						
70–74	1,820	(25)						
≥ 75	1,033	(14)						
Mean (5th, 95th percentiles)	68.3 (58.0, 78.1)							
Educational level			0.48	0.79	0.48	0.74	0.20	0.28
Basic	2,248	(31)						
Vocational	3,110	(42)						
Higher	1,868	(26)						
Unknown	94	(1)						
Cohabitation			0.05	0.31	0.10	0.64	0.98	0.90
Living alone	2,304	(31)						
Living with partner	5,011	(68)						
Unknown	5	(0)						
Charlson Comorbidity Index score			0.61	0.89	0.22	0.75	0.83	0.03
0	4,846	(66)						
1	1,516	(21)						
≥2	958	(13)						
Treated for depression before cancer								

Depress Anxiety. Author manuscript; available in PMC 2018 September 01.

			Test for differences in baseline characteristics (*P*)					
			5-HTTLPR genotypes					
	n	**(%)**	**Biallelic**	**Triallelic**	**BDNF**	**HTR1A**	**COMT**	**FKBP5**
No	6,478	(89)	0.47	0.25	0.66	0.49	0.67	0.92
Yes	842	(12)						
Calendar year of diagnosis			0.31	0.21	0.55	0.93	0.32	0.40
Median (Q1, Q3)	2007 (2003 (2010)							
Site of cancer			0.95	1.00	0.53	0.98	0.32	0.34
Prostate	1,873	(25)						
Breast	1,662	(23)						
Corpus uteri	259	(4)						
Ovarian	196	(3)						
Urinary bladder	578	(8)						
Colorectal cancer	1,282	(18)						
Lung, bronchus and trachea	1,155	(16)						
Pancreas	315	(4)						

Differences between genotypes within genetic variants were tested for people successfully genotyped for each variant. We used χ^2 tests for categorical variables, while calendar year of diagnosis was tested with ANOVA.

TABLE 2

Distribution of genotypes within genetic variants and Cox analyses of associations between genotypes and treatment with antidepressants and hospital contact for depression after cancer among all 7,320 people in the Diet, Cancer and Health cohort study with one of eight major cancer types diagnosed in 1998–2013

				Treatment with antidepressants					Hospital contact for depression				
	Genotype	***N***	**(%)**	**Person-years**	**Events**	**HR**	**99.58% CI**	***P***	**Person-years**	**Events**	**HR**	**99.58% CI**	***P***
5-HTTLPR, biallelic	LL	2459	(34)	9,191	588	1	–	–	11 075	31	1	–	–
	SL	3439	(48)	12,627	803	0.99	0.84–1.15	0.80	14,959	45	1.04	0.54–2.04	.85
	SS	1262	(18)	4,609	321	1.07	0.88–1.31	0.33	5,655	17	1.05	0.44–2.50	.87
5-HTTLPR, triallelic	L_AL_A	1882	(27)	6,966	458	1	–	–	8,425	27	1	–	–
	L_AL_G, SL_A	3441	(49)	12,763	789	0.95	0.80–1.12	0.33	15,069	45	0.91	0.45–1.82	.69
	L_GL_G, SL_G, SS	1714	(24)	6,326	429	1.02	0.85–1.24	0.73	7,693	20	0.80	0.34–1.87	.45
BDNF	GG	4576	(64)	16,897	1080	1	–	–	20,220	57	1	–	–
	AG	2313	(32)	8,557	560	1.03	0.88–1.19	0.62	10,331	34	1.16	0.62–2.16	.50
	AA	317	(4)	1,161	75	1.01	0.72–1.42	0.93	1,340	3	0.82	0.15–4.48	.74
HTR1A	CC	1835	(25)	6,637	434	1	–	–	8,651	22	1	–	–
	GC	3595	(50)	13,412	840	0.97	0.82–1.15	0.57	15,984	43	1.01	0.48–2.15	0.9
	GG	1779	(25)	6,602	449	1.05	0.86–1.27	0.49	7,925	28	1.35	0.60–3.07	0.29
COMT	GG	1399	(19)	5,419	331	1	–	–	6,461	22	1	–	–
	GA	3606	(50)	13,474	849	0.99	0.82–1.19	0.83	15,995	43	0.73	0.34–1.86	0.22
	AA	2207	(31)	7,748	540	1.06	0.87–1.30	0.40	9,482	28	0.82	0.36–1.54	0.49
FKBP5[a]	CC	3181	(51)	11,414	753	1	–	–	13,721	39	1	–	–
	CT	2542	(40)	8,974	610	1.04	0.89–1.21	0.53	10,817	39	1.29	0.67–2.46	0.27
	TT	562	(9)	2,010	140	1.07	0.82–1.39	0.49	2,470	7	1.08	0.33–3.50	0.85

[a]FKBP5 was genotyped in only a subpopulation of 6,408 people.