Reduced cancer incidence in Huntington's disease: analysis in the Registry study

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Running title: Reduced cancer incidence in HD

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Abstract

BACKGROUND People with Huntington's disease have been observed to have lower rates of cancers.

OBJECTIVE To investigate the relationship between age of onset of HD, CAG repeat length and cancer diagnosis. METHODS Data were obtained from the European Huntington's disease network REGISTRY study for 6540 subjects. Population cancer incidence was ascertained from the GLOBOCAN database to obtain standardised incidence ratios of cancers in the REGISTRY subjects.

RESULTS 173/6528 HD REGISTRY subjects had had a cancer diagnosis. The age-standardised incidence rate of all cancers in the REGISTRY HD population was 0.26 (CI 0.22-0.30). Individual cancers showed a lower age-standardised incidence rate compared with the control population with prostate and colorectal cancers showing the lowest rates. There was no effect of CAG length on the likelihood of cancer, but a cancer diagnosis within the last year was associated with a greatly increased rate of HD onset (Hazard Ratio 18.94, $p<0.001$).

CONCLUSIONS Cancer is less common than expected in the HD population, confirming previous reports. However, this does not appear to be related to CAG length in HTT. A recent diagnosis of cancer increases the risk of HD onset at any age, likely due to increased investigation following a cancer diagnosis.

Keywords:

Huntington's disease

Trinucleotide repeat

Cancer

Neurodegeneration

Introduction

Huntington's disease (HD) is an inherited neurodegeneration of mid-life onset. It is caused by an expanded CAG repeat at the 5' end of the *HTT* gene, which is translated to give a polyglutamine tract at the N-terminus of the encoded protein, huntingtin (HTT) (1). It is characterised by a movement disorder, cognitive decline and variable psychiatric symptoms with early and continuing cell death in the striatum(1,2). The disease is inexorably progressive and there is no treatment that can prevent the neurodegeneration(2).

Studies in the systematic population registries of the Scandinavian countries show a reduction in the expected age-matched incidence of cancer in subjects with a diagnosis of HD and spinal and bulbar muscular atrophy (SBMA, Kennedy's disease) another disease caused by an expanded CAG tract(3,4). Scandinavian countries have country-wide registers that record whole population health so mining these data can be potentially very productive. Most countries do not have such comprehensive and well maintained registers and thus it is hard to replicate such studies. However, the Oxford Record Linkage Group examined rates of cancers in an all-England population study, the English linked hospital episode statistics (LHES), 1999–2010, and showed a similar effect(5). They examined HD, SBMA, and a larger group of hereditary ataxias (HA), which include the CAG repeat expansion associated spino-cerebellar ataxias (SCAs). The rate ratio cancer diagnosis in 4865 people with HD was 0.53, with no effect seen in subjects with a diagnosis of SBMA or HA. More recently Coarelli et al. (6) questioned a cohort of HD and SCA patients directly about their experience of cancer and found standardised incidence ratios of 0.21 in HD and 0.23 in SCAs.

A reduction in cancer incidence is seen in other neurodegenerative conditions. A systematic examination of records from over 500,000 subjects in observational studies of CNS disorders showed a robust lower cancer co-occurrence in all neurodegenerations, with strikingly significantly lower rates in Alzheimer's disease (ES 0.32)(7). Their HD data was derived from Ji and Sorensen(3,4). By contrast Freedman et al.(8) observed only a modestly reduced risk of Alzheimer's disease in cancer

survivors in a prospective analysis of 1.16 million subjects in a Medicare population (HR = 0.87 (95% CI = 0.84-0.90). To follow up these studies we examined the incidence of cancers in the EHDN REGISTRY study directly. We obtained the data from REGISTRY and the population rates from the Globocan study(9). We also examined the effect of the CAG length and the age of onset of HD on cancer incidence.

Materials and Methods

Participants

Data were provided from 6540 subjects participating in the REGISTRY study of the European Huntington's Disease Network (EHDN) prior to June 2013. 12 subjects originated in South East Asia and were excluded, giving 6528 subjects in the final study. REGISTRY is a large, prospective study observing the natural course, clinical spectrum and management of HD in European countries. More information on the REGISTRY study can be found at (http://www.euro-hd.net/html/REGISTRY). All experiments were performed in accordance with the Declaration of Helsinki, full ethical approval for the REGISTRY study was obtained in each of the participating countries, and all participants gave written informed consent. The information includes demographics, HD related CAG repeat length, age at onset of HD, cancer and comorbidity, and medication data. Whilst we obtained data on other aspects of medical history and on alcohol use, smoking, drug abuse and employment we did not use these in analysis as the numbers of cancer patients were relatively low and only 4 subjects were recorded as having a history of lung cancer, for instance. Thus further subdivision of the sample was not deemed useful. Country of clinical site was obtained to adjust for country-specific cancer incidence with the UK, Spain, France, Germany, Italy, Poland given directly and a “Europe” category for all those from countries contributing relatively few subjects. Incidences of cancer were identified by searching for "cancer", "carcinoma" and "malignant neoplasm" in the comorbidity data field and cross-checked using the ICD10 codes given: 171 patients were identified. To provide some confirmation of the cancer diagnosis we looked for subjects taking medication specific for cancers

and 25/171 (14.6%) were confirmed by medication. However, this search also identified two patients taking cancer-specific therapies who did not have cancer listed as a co-morbidity. In the final sample we had 173 subjects with evidence for a diagnosis of cancer.

Comparison of age-standardised cancer incidence

In order to ascertain whether the number of cancer cases is more or less than might be expected we compared these data with age-adjusted cancer incidence from Europe available on the GLOBOCAN website (http://globocan.iarc.fr): the data used for the analysis were from 2012 (9) as the REGISTRY data were obtained in June 2013 and thus reflected data captured in the period 2012-13.

The age-standardised incidence rate (SIR) was calculated (equation 1). Person-years were calculated from date of birth until date of diagnosis of cancer or the end of the study period (whichever came first), then the ratio of observed number of cases to expected number of cases was calculated but adjusted for age and sex. This is important in this analysis as the REGISTRY cohort is substantially younger than those at highest risk for cancers in the European population and cancer incidence is age-related.

Equation 1

$$SIR = \frac{\sum_{j=1}^{J} o_j}{\sum_{j=1}^{J} n_j \lambda_j} = \frac{O}{E^*}$$

O = observed cancer cases in the study group (173), *E** = sum of stratum-specific person years (n_j) in subjects with HD x stratum-specific standard incidence rates (λ_j*) obtained from the GLOBOCAN reference group(9). The age stratification is given in Table 1. The weighting was adjusted to reflect the proportions of different countries amongst the 6528 HD subjects.

Relationship of cancer incidence to *HTT* CAG repeat length and age at onset of HD

We analysed time from birth to HD onset using Cox proportional hazards models (10), adjusting for a time-varying covariate defined to be 0 until a person received a cancer diagnosis, and 1 thereafter. The effect of this is to compare, at every age, the rate of HD onset between those with, and without, a previous cancer diagnosis. This corrects for the fact that people with cancer are likely to be older (since they have lived long enough to develop cancer) than those without, and thus to have a later HD onset, since their HD incidence rates are being compared to people of the same age without a cancer diagnosis. A Cox proportional hazard model was used to assess whether CAG repeat length was related to the age of cancer incidence, with adjustment for sex and stratification by country. We also assessed whether a cancer diagnosis influenced the age of onset of HD.

To investigate the possibility that a cancer diagnosis may quickly bring about increased investigation of HD symptoms, and thus an apparent increase in HD incidence rate, we also included a time-varying covariate that was only 1 during the year immediately following a cancer diagnosis, and 0 elsewhere.

Results

There were 6540 patients identified from the EHDN REGISTRY study(11) with appropriate data: details are given in Table 1. Eight subjects were excluded as they were collected outside Europe (Singapore) and four had incomplete records. The 6528 subjects remaining were collected in European clinics, had a clinical diagnosis of HD and 173 (2.65%) of these patients also had information consistent with a cancer diagnosis. In the whole cohort 52.6% of subjects are female and 47.4% male. There is a higher proportion of females amongst those with a diagnosis of cancer than in those without (Table 1): this is attributable to the relative youth of our HD sample as the incidence of breast cancer is higher at relatively young ages compared with many other cancers. The sample size is too small to split by specific cancers to explore this further. The average age of the non-cancer HD subjects at the point of data collection (age at last visit) is over 10 years younger than in those with a cancer diagnosis and the mean CAG repeat length is longer in the non-cancer cohort than in the subjects with cancer (Table 1).

The distribution of the cancer diagnoses in the 173 subjects is given in Table 2. The standardised incidence rate (SIR) of cancers in the HD population was calculated (Table 2) and for all cancers was 0.26 (CI 0.22 – 0.30). All cancers were observed at significantly lower levels than in the European population though there were differences in the rates between the types of cancer. Uterine and skin cancers had age-standardised incidence rates closest to the European levels with colorectal, breast and prostate cancer all recorded at less than half the rates in the European population.

Those with a cancer diagnosis have, on average, over 10 years later age of onset of HD than those without. Testing whether this is significantly different, is, as noted above, complicated by the fact that cancer incidence rises as people age, and those with later ages of onset of HD will, on average, live longer and thus be more likely to develop a cancer(12). Modelling this using a cancer diagnosis at any time in the past as a time-dependent covariate in a Cox proportional hazards model(10) of time to HD onset, shows that those with a cancer diagnosis at any age are very slightly more likely to have HD onset than those without cancer at the same age (HR 1.2773; 95% CI 1.06 to 1.61, $p < 0.001$). A cancer diagnosis during the past year is strongly associated with an increased rate of HD onset (HR 18.95, 95% CI 13.01 to 23.20, $p < 0.001$).

As we noted that the subjects with cancer diagnoses have shorter CAG repeat lengths than those without (Table 1), we investigated whether this is significantly associated with the likelihood of developing cancer. Given that the CAG repeat showed the expected significant inverse correlation with age of HD onset ($p < 2x10^{-16}$), the apparent association of cancer with CAG length could be a result of people with shorter CAG repeats on average living longer (as age at death in HD is inversely correlated with expanded *HTT* allele CAG repeat length), and thus having a greater risk of developing cancer(12). To test whether this bias in lifetime length accounts for the apparent association between CAG length and cancer diagnosis we used a Cox proportional hazards model (10) with time from birth to cancer diagnosis as an outcome (death and HD diagnosis both as censoring) and CAG

length as a covariate. We also adjusted for age and sex and used different baseline hazards for the different countries. There are no discernible effects of CAG repeat length on cancer incidence.

Discussion

The standardised incidence ratio for all cancers detected in the REGISTRY subjects is substantially lower than that in the non-HD population, as reported previously(3–6). Cancer might be underdiagnosed in the HD population in later stages of the illness as potentially relevant signs or symptoms may not be noticed or acted upon, or may be masked by HD symptoms – cachexia for instance, common in cancers, is also common in late stage HD. Our findings in the REGISTRY study show a lower rate of cancers than that reported in previous studies of cancer in HD subjects in population cohorts (3–5) which could indicate under-ascertainment of cancer in our sample. However, the recent study examining French HD and SCA populations and asking directly about cancer show a similar SIR to that which we show in this study(6). However, it is also likely that having a diagnosis of HD, and therefore coming to clinical attention, makes diagnosis of any comorbidities more likely. Turner et al.(5), studying hospital admission records in England, found that there was an increased rate of cancer diagnoses in the first year after admission for HD. The overall decrease in the rate of cancers that they observed among HD patients (rate ratio = 0.71) was made more extreme if the first year was excluded (rate ratio = 0.53). This indicates that under-diagnosis is less likely in this population, rather than more likely: we showed a similar effect in the REGISTRY subjects. The only cancer they found to be as common as in the general population was lung cancer, which Turner *et al.*(5) attributed to the higher rate of smoking in the HD subjects(13). We had only four cases of lung cancer in our study, too few to study separately.

The observation that two subjects were taking tamoxifen but had no recorded cancer diagnosis indicates that one of the reasons for the lower rate of all cancers observed here might well be poor recording of comorbidities in the REGISTRY database. This could result from poor recall of the participant, lack of knowledge of their partners and carers in clinic or from subjects dropping out of

the study after a diagnosis of cancer due to treatment or other effects of the cancer itself and issues in the systematic collection of medical history in clinic.

In an attempt to overcome the limitations of these data we investigated the effect of CAG repeat length on the time to a cancer diagnosis with the view that any correlation might implicate the CAG length at the *HTT* locus in promoting or delaying cancer. No such effect was observed. To further investigate any link between the two diseases we also examined whether having a cancer diagnosis was associated with age at onset of HD. This is more difficult as there are competing risks: cancer risk is age-related, and a cancer diagnosis may influence time to death as well as time to HD onset, as may *HTT* CAG length. However, we observe that a diagnosis of cancer at any time slightly increases the likelihood of HD onset: this marginal effect requires replication in further studies. In addition, the study of Turner *et al.*(5) found that cancer incidences were higher in the year around HD onset and we see a similar effect in the REGISTRY data. This latter is likely to be an ascertainment bias: subjects receiving clinical attention are more likely to have any comorbid condition detected and therefore under-diagnosis of cancer is less likely in this population.

What might underlie the later onset of cancer in HD subjects? Defects in the DNA damage response (DDR) cause cancers (14) and the DDR has recently been implicated in altering the age at motor onset of HD and other repeat disorders (15,16). The direction of this effect is unclear and alterations in the operation of the DDR have been shown to be both protective and deleterious in HD and other neurodegenerations. Mismatch repair and base-excision repair have both been implicated as promoting degeneration in the repeat disorders, possibly through somatic expansion of repeats (17,18). Many other neurological diseases are caused by genetic defects in the DDR (19) but conversely, multiple protective effects of the DDR in neurodegenerations have also been observed (20–27).

One consequence of the involvement of the DDR in modifying HD onset might be that although age at onset is later in subjects who have had a cancer diagnosis, if they have cancer in the presence of

lower DDR activity, then that cancer might be more aggressive with a faster course. HTT has been implicated in acceleration of breast cancer development and metastasis in mouse models of HD and to regulate cell division in mammary stem cells (28) . In subjects with breast cancer a reduction of ovarian cancer was shown in *BRCA2* mutation carriers also carrying longer *HTT* CAGs(29), along with a paradoxical finding of increased metastasis and younger ages of cancer onset. Direct examination of metastatic breast cancer showed *HTT* mRNA downregulation in primary tumours and that the expression and localisation of the tight junction protein ZO1 was controlled by HTT(30). Lower expression of HTT was correlated with less HTT and ZO1 proteins at tight junctions, poorer differentiation of tumour cells and was predictive of worse cancer prognosis(31).

It is not clear how the effect of increased CAG repeats, which translate to expanded polyglutamine tracts in the cognate proteins, could potentially mediate cancer risk but the underlying biology of HD offers clues. Huntingtin (HTT) is expressed in all cells: cell death is promoted by mutant HTT (32–34) and non-mutant HTT is anti-apoptotic(35). HTT localises to spindle poles at mitosis and has a role in cell fate in neurons(36) that may extend to other cell types: therefore in neuronal cells it has been suggested that HTT regulates the balance between survival and death. Most of the experimental work examining these functions has only looked at long (>40) CAGs compared with a single normal range CAG length thus our knowledge of the downstream effects of small differences in the CAG repeat length below 40 CAGs on HTT biology are limited. If small modulations in CAG length in HTT and potentially other genes containing polymorphic CAG repeats impose a relatively small effect on cell fate decisions over a long period then they could well be one of the multiple factors that influence whether a cell divides or dies, contributing to the risk of uncontrolled cell division. The effect could in part be explained by the RNA generated from the expanded CAG repeat in *HTT*. sCAGs are small CAG repeat RNAs generated from the *HTT* gene (37) which are toxic to neurons (38) and may operate via an RNAi-based mechanism and downregulate trinucleotide repeat-containing survival genes, leading to tumour cell death (39). Similar findings in other neurodegenerative diseases(7) might implicate a broader biological relationship between cell survival and cell death in

the CNS, manifesting as neurodegeneration. Thus determining the relationship between CAG length in *HTT* and other polymorphic CAG repeat loci could well reveal fundamental biological mechanisms underlying both cancer risk and neurodegeneration.

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Author contributions

The REGISTRY Investigators of the European Huntington's Disease Network collected the data. PM, RP, RR, RN and DF analysed the data, AH assisted in interpreting the clinical data, PH and DF supervised the data analysis, LJ conceived the study and wrote the main manuscript text. All authors reviewed the manuscript.

Conflict of Interest

The authors declare no competing financial interests.

References

1. Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, et al. Huntington disease. Nat Rev Dis Prim [Internet]. 2015 Apr 23 [cited 2016 Apr 18];1:15005. Available from: http://www.nature.com/articles/nrdp20155
2. Ross CA, Tabrizi SJ. Huntington's disease: From molecular pathogenesis to clinical treatment. Lancet Neurol. 2011;10(1):83–98.
3. Sørensen SA, Fenger K, Olsen JH. Significantly lower incidence of cancer among patients with Huntington disease: An apoptotic effect of an expanded polyglutamine tract? Cancer [Internet]. 1999 Oct 1 [cited 2016 Apr 18];86(7):1342–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10506723

4. Ji J, Sundquist K, Sundquist J. Cancer incidence in patients with polyglutamine diseases: a population-based study in Sweden. Lancet Oncol [Internet]. 2012 Jun [cited 2016 Apr 18];13(6):642–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22503213

5. Turner MR, Goldacre R, Goldacre MJ. Reduced cancer incidence in Huntington's disease: record linkage study clue to an evolutionary trade-off? Vol. 83, Clinical genetics. Denmark; 2013. p. 588–90.

6. Coarelli G, Diallo A, Thion MS, Rinaldi D, Calvas F, Boukbiza OL, et al. Low cancer prevalence in polyglutamine expansion diseases. Neurology. United States; 2017 Mar;88(12):1114–9.

7. Catala-Lopez F, Suarez-Pinilla M, Suarez-Pinilla P, Valderas JM, Gomez-Beneyto M, Martinez S, et al. Inverse and direct cancer comorbidity in people with central nervous system disorders: a meta-analysis of cancer incidence in 577,013 participants of 50 observational studies. Psychother Psychosom. Switzerland; 2014;83(2):89–105.

8. Freedman DM, Wu J, Chen H, Kuncl RW, Enewold LR, Engels EA, et al. Associations between cancer and Alzheimer's disease in a U.S. Medicare population. Cancer Med. United States; 2016 Oct;5(10):2965–76.

9. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J cancer. United States; 2015 Mar;136(5):E359-86.

10. Cox DR. Regression Models and Life-Tables. J R Stat Soc Ser B. 1972;34(2):187–220.

11. Orth M, Network TEH 's D. Observing Huntington's disease: the European Huntington's Disease Network's REGISTRY. J Neurol Neurosurg Psychiatry [Internet]. 2011 Dec 1;82(12):1409–12. Available from: http://jnnp.bmj.com/content/82/12/1409.short

12. Keum JW, Shin A, Gillis T, Mysore JS, Abu Elneel K, Lucente D, et al. The HTT CAG-Expansion Mutation Determines Age at Death but Not Disease Duration in Huntington Disease. Am J Hum Genet. United States; 2016 Feb;98(2):287–98.

13. Ehret JC, Day PS, Wiegand R, Wojcieszek J, Chambers RA. Huntington disease as a dual diagnosis disorder: data from the National Research Roster for Huntington disease patients and families. Drug Alcohol Depend. Ireland; 2007 Jan;86(2–3):283–6.

14. Pearl LH, Schierz AC, Ward SE, Al-Lazikani B, Pearl FMG. Therapeutic opportunities within the DNA damage response. Nat Rev Cancer. England; 2015 Mar;15(3):166–80.

15. Huntington's GM of, Disease Consortium (GeM-HD). Identification of Genetic Factors that Modify Clinical Onset of Huntington's Disease. Cell [Internet]. 2015;162(3):516–26. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0092867415008405

16. Bettencourt C, Moss DH, Flower M, Wiethoff S, Brice A, Goizet C, et al. DNA repair pathways underlie a common genetic mechanism modulating onset in polyglutamine diseases. Ann Neurol [Internet]. 2016 Apr 4 [cited 2016 Apr 18]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/27044000

17. Budworth H, Harris FR, Williams P, Lee DY, Holt A, Pahnke J, et al. Suppression of Somatic Expansion Delays the Onset of Pathophysiology in a Mouse Model of Huntington?s Disease. PLoS Genet [Internet]. Public Library of Science; 2015 Aug 6;11(8):e1005267. Available from: http://dx.doi.org/10.1371%2Fjournal.pgen.1005267

18. Schmidt MHM, Pearson CE. Disease-associated repeat instability and mismatch repair. DNA Repair (Amst) [Internet]. 2016 Feb [cited 2016 Apr 18];38:117–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26774442

19. McKinnon PJ. DNA repair deficiency and neurological disease. Nat Rev Neurosci [Internet]. Nature Publishing Group; 2009 Feb;10(2):100–12. Available from: http://dx.doi.org/10.1038/nrn2559

20. Suberbielle E, Sanchez PE, Kravitz A V, Wang X, Ho K, Eilertson K, et al. Physiologic brain activity causes DNA double-strand breaks in neurons, with exacerbation by amyloid-beta. Nat Neurosci. United States; 2013 May;16(5):613–21.

21. Suberbielle E, Djukic B, Evans M, Kim DH, Taneja P, Wang X, et al. DNA repair factor BRCA1 depletion occurs in Alzheimer brains and impairs cognitive function in mice. Nat Commun. England; 2015;6:8897.

22. Illuzzi J, Yerkes S, Parekh-Olmedo H, Kmiec EB. DNA breakage and induction of DNA damage response proteins precede the appearance of visible mutant huntingtin aggregates. J Neurosci Res. United States; 2009 Feb;87(3):733–47.

23. Qi M-L, Tagawa K, Enokido Y, Yoshimura N, Wada Y, Watase K, et al. Proteome analysis of soluble nuclear proteins reveals that HMGB1/2 suppress genotoxic stress in polyglutamine diseases. Nat Cell Biol. England; 2007 Apr;9(4):402–14.

24. Enokido Y, Tamura T, Ito H, Arumughan A, Komuro A, Shiwaku H, et al. Mutant huntingtin impairs Ku70-mediated DNA repair. J Cell Biol. United States; 2010 May;189(3):425–43.

25. Jeon GS, Kim KY, Hwang YJ, Jung M-K, An S, Ouchi M, et al. Deregulation of BRCA1 leads to impaired spatiotemporal dynamics of gamma-H2AX and DNA damage responses in Huntington's disease. Mol Neurobiol. United States; 2012 Jun;45(3):550–63.

26. Ito H, Fujita K, Tagawa K, Chen X, Homma H, Sasabe T, et al. HMGB1 facilitates repair of mitochondrial DNA damage and extends the lifespan of mutant ataxin-1 knock-in mice. EMBO Mol Med. England; 2015 Jan;7(1):78–101.

27. Jones L, Houlden H, Tabrizi SJ. DNA repair in the trinucleotide repeat disorders. Lancet Neurol. 2017;16:88–96.

28. Moreira Sousa C, McGuire JR, Thion MS, Gentien D, de la Grange P, Tezenas du Montcel S, et al. The Huntington disease protein accelerates breast tumour development and metastasis through ErbB2/HER2 signalling. EMBO Mol Med. England; 2013 Feb;5(2):309–25.

29. Thion MS, Tezenas du Montcel S, Golmard J-L, Vacher S, Barjhoux L, Sornin V, et al. CAG repeat size in Huntingtin alleles is associated with cancer prognosis. Eur J Hum Genet. 2016 Mar;

30. Elias S, Thion MS, Yu H, Sousa CM, Lasgi C, Morin X, et al. Huntingtin regulates mammary stem cell division and differentiation. Stem cell reports. United States; 2014 Apr;2(4):491–506.

31. Thion MS, McGuire JR, Sousa CM, Fuhrmann L, Fitamant J, Leboucher S, et al. Unraveling the Role of Huntingtin in Breast Cancer Metastasis. J Natl Cancer Inst. United States; 2015 Oct;107(10).

32. Grison A, Mantovani F, Comel A, Agostoni E, Gustincich S, Persichetti F, et al. Ser46

phosphorylation and prolyl-isomerase Pin1-mediated isomerization of p53 are key events in p53-dependent apoptosis induced by mutant huntingtin. Proc Natl Acad Sci U S A. United States; 2011 Nov;108(44):17979–84.

33. Ghose J, Sinha M, Das E, Jana NR, Bhattacharyya NP. Regulation of miR-146a by RelA/NFkB and p53 in STHdh(Q111)/Hdh(Q111) cells, a cell model of Huntington's disease. PLoS One. United States; 2011;6(8):e23837.

34. Zuccato C, Valenza M, Cattaneo E. Molecular mechanisms and potential therapeutical targets in Huntington's disease. Physiol Rev. United States; 2010 Jul;90(3):905–81.

35. Rigamonti D, Bauer JH, De-Fraja C, Conti L, Sipione S, Sciorati C, et al. Wild-type huntingtin protects from apoptosis upstream of caspase-3. J Neurosci. UNITED STATES; 2000 May;20(10):3705–13.

36. Godin JD, Colombo K, Molina-Calavita M, Keryer G, Zala D, Charrin BC, et al. Huntingtin is required for mitotic spindle orientation and mammalian neurogenesis. Neuron. United States; 2010 Aug;67(3):392–406.

37. Bañez-Coronel M, Ayhan F, Tarabochia AD, Zu T, Perez BA, Tusi SK, et al. RAN Translation in Huntington Disease. Neuron [Internet]. 2015 Nov 18;88(4):667–77. Available from: http://www.sciencedirect.com/science/article/pii/S0896627315009320

38. Rue L, Banez-Coronel M, Creus-Muncunill J, Giralt A, Alcala-Vida R, Mentxaka G, et al. Targeting CAG repeat RNAs reduces Huntington's disease phenotype independently of huntingtin levels. J Clin Invest. United States; 2016 Nov;126(11):4319–30.

39. Murmann AE, Gao QQ, Putzbach WE, Patel M, Bartom ET, Law CY, et al. Small interfering RNAs based on huntingtin trinucleotide repeats are highly toxic to cancer cells. EMBO Rep. England; 2018 Mar;19(3).

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Table 1 Characteristics of those with and without a cancer diagnosis in the REGISTRY cohort

Age	**Non-cancer patients**	**Cancer patients**
	n=6355	n= 173
0 to 10	1 (0.02%)	0 (0%)
11 to 20	14 (0.2%)	0 (0%)
21 to 30	373 (5.9%)	0 (0%)
31 to 40	942 (14.8%)	2 (1.2%)
41 to 50	1588 (25.0%)	14 (8.1%)
51 to 60	1621 (25.5%)	36 (20.8%)
61 to 70	1218 (19.2%)	57 (33.0%)
71 to 80	502 (7.9%)	53 (30.6%)
81 to 90	92 (1.5%)	10 (5.8%)
91 to 100	4 (0.06%)	1 (0.6%)
Average	52.1	66.0
M/F	3009/3346 (47.4%)	62/111 (64.2%)
CAG Repeat Length	44.1 (±4.2) n=5029	42.1 (±2.3) n=173
Age at onset HD	45.7 (±13.9) n=6354	58.0 (±10.7) n=154

Table 2 Standardised incidence rates of cancers in the REGISTRY population

Cancer site	SIR (95% CI)	# Cases
Breast	0.37 (0.26-0.48)*	44
Prostate	0.30 (0.17-0.43)*	20
Skin	0.59 (0.33-0.85)*	20
Uterus	0.66 (0.36-0.96)*	19
Colorectal	0.26 (0.13-0.39)*	16
Kidney	0.40 (0.12-0.68)*	8
Other Sites	0.19 (0.13-0.24)*	46
All	**0.26 (0.22-0.30)***	**173**

SIR = standardised incidence rate. CI = confidence interval. *significantly different from expected. Other sites include ovary (8), lung (4), bladder (4), brain (3), thyroid (3), liver/bile duct (3) and stomach (3).