Cancer and hereditary hemorrhagic telangiectasia

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Word Count: 500

Tables/Figures :0

References:8

ABSTRACT

OBJECTIVE: To examine associations between cancer incidence and hereditary hemorrhagic telangiectasia (HHT).

METHODS: Two studies with contrasting conclusions were compared. The first had used a registry-based, matched pairs approach, while the second utilised HHT-family based, survey methodology.

RESULTS: The first manuscript captured data on cancer incidence in a total of 316,581 matched cancer patients-non cancer controls, which included 431 HHT cases. No association was found between HHT and pooled cases of lung, breast, prostate and colorectal cancer (adjusted OR 0.978, 95% CI (0.795. 1.204). The second, which was powered to examine these four cancers individually, captured data from 2,161 HHT-affecteds, 2,817 related controls, and resulted in very different conclusions: Fewer HHT-affected individuals had cancer (398/2,161, (18.4%) compared to 668/2,817 (23.7%) related controls (p=0.0012). Of the four most common cancers, prostate and colorectal cancer rates were equivalent, but lung cancers were significantly less frequent in HHT (adjusted OR 0.48 [0.30, 0.70], p=0.0012); and breast cancer more frequent (adjusted OR 1.52 [1.07, 2.14] p=0.018).

CONCLUSIONS: The respective studies had different methodological strengths and weaknesses. Potential reasons for the discrepant conclusions include study power, particularly important to dissect specific cancers where differential contributions from HHT genotypes and environmental confounders might be predicted.

To the Editor,

We read with interest the recent paper (Duarte 2016) that examined associations between cancer incidence and hereditary haemorrhagic telangiectasia (HHT). HHT is a vascular dysplasia, usually caused by a pathogenic DNA sequence variant in *ENG* (encoding endoglin), or *ACVRL1 (*encoding ALK1). A small proportion of HHT families have causative DNA sequence variants in *SMAD4*, associated with juvenile polyposis and increased risk of colorectal and other cancers.

Following demonstration of better survival outcomes for HHT cancer patients (Duarte 2014), the authors examined cancer incidence, pooling lung, breast, prostate and colorectal cancer. Using a general population registry, 316,581 matched cancer patients and non-cancer controls were identified, including 219 and 212 HHT cases respectively. Crude categorical analyses, and adjusted conditional logistic regression, demonstrated no association between cancer incidence and HHT (adjusted odds ratio 0.978, 95% CI (0.795, 1.204), (Duarte 2016).

We also examined cancer incidence in HHT (Hosman 2013), based on unexpectedly well preserved life expectancy in HHT (Kjeldsen 1999). To capture a greater number of HHT-affecteds, and control for some of the plethora of cancer susceptibility alleles and shared environmental exposures segregating within families, we used HHT family-based methodology. In addition, our study differed as it was powered to look at the top 4 primary cancers individually, examining cancer incidence in 2,161 HHT-affecteds, and 2,817 controls, who were the parent and grandparent(s) who could not have HHT, based on autosomal dominant inheritance. Our survey-based methodology could not distinguish between primary and secondary tumours. However, for 15 “predominantly primary” cancers, the

incidence of different cancers per 100,000 controls per year was similar to ASRs for the Developed World (Globocan 2008), validating study methodology (Hosman 2013).

Our results led to very different conclusions and implications (Hosman 2013). In crude analyses, fewer cancers were reported for HHT patients (398/2161, 18.4%) than controls (668/2817, 23.7%, p=0.0012). Importantly, the attributable effect of HHT differed between the 4 cancers.

In both crude and age-adjusted regression, lung cancers were significantly less frequent in the HHT arm than controls (age-adjusted odds ratio 0.48 [0.30, 0.70], p=0.0012). This was despite higher smoking exposure in the HHT population.

Breast cancer prevalence was higher in HHT than controls (age-adjusted OR 1.52 [1.07, 2.14], p=0.018), with one proposed confounder being greater exposure to iatrogenic radiation in the HHT group.

Prostate and colorectal cancer rates were equivalent, but the pattern of colorectal cancer was modified: A higher prevalence in younger HHT patients than controls was attributed to the HHT patients with *SMAD4* pathogenic variants associated with increased risk of colorectal cancer (Jelsig 2016).

We fully recognise the limitations of survey-based study methodologies (Hosman 2013), but do consider that appropriately powered studies are essential within rare diseases in order to provide informative data to guide patient management and focus future research. For HHT, it is important not

only to recognise the inhomogeneity of the population in terms of HHT and wider genotypes, but also to adjust for important confounding variables such as smoking, iatrogenic radiation exposure,(Hanneman 2014) and potentially even iron treatments for anemia (Mollet 2016).

Declarations:

AEH and CLS declare that they have no conflict of interests.

There is no funding to report for the manuscript.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research ethics service (NRES) Committee East Midlands-Derby 1 Research Ethics Committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the reported study

References:

1) Duarte CW, Black AW, Lucas FL, Vary CP (2016). Cancer incidence in patients with hereditary hemorrhagic telangiectasia. J Cancer Res Clin Oncol [Epub ahead of print].

2) Duarte CW, Murray K, Lucas FL, Fairfield K, Miller H, Brooks P, Vary CP (2014). Improved survival outcomes in cancer patients with hereditary hemorrhagic telangiectasia.Cancer Epidemiol Biomarkers Prev 23(1):117-25.

3) Hosman AE, Devlin HL, Silva BM, Shovlin CL (2013). Specific cancer rates may differ in patients with hereditary haemorrhagic telangiectasia compared to controls. Orphanet J Rare Dis 20;8:195.

4) Kjeldsen AD, Vase P, Green A (1999). Hereditary haemorrhagic telangiectasia: a population-based study of prevalence and mortality in Danish patients. J Intern Med 245:31–39.

5) GLOBOCAN 2008: Estimated cancer Incidence, Mortality, Prevalence and Disability-adjusted life years (DALYs) Worldwide in 2008 [http://globocan.iarc.fr], Globocan 2012 accessed 17.10.2016.

6) Jelsig AM, Tørring PM, Kjeldsen AD, Qvist N, Bojesen A, Jensen UB, Andersen MK, Gerdes AM, Brusgaard K, Ousager LB (2016). JP-HHT phenotype in Danish patients with SMAD4 mutations. Clin Genet 90(1):55-62.

7) Hanneman K, Faughnan ME, Prabhudesai V (2014). Cumulative radiation dose in patients with hereditary hemorrhagic telangiectasia and pulmonary arteriovenous malformations. Can Assoc Radiol J 65(2):135-40.

8) Mollet IG, Patel D, Govani FS, Giess A, Paschalaki K, Periyasamy M, Lidington EC, Mason JC, Jones MD, Game L, Ali S, Shovlin CL (2016). Low dose iron treatments induce a DNA damage response in human endothelial cells within minutes. PLoS One 11(2):e0147990.