Review

Frequency of CDH1 Germline Mutations in Non-Gastric Cancers

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Simple Summary: Diffuse gastric cancer is the hallmark of the hereditary diffuse gastric cancer syndrome related with the E-cadherin germline mutations. Other cancers (non-gastric) are described in association with the CDH1 gene germline alterations. In this study, we aimed to assess the overall frequency of CDH1 mutations in non-gastric tumors reported in literature so far.

Abstract: Hereditary Diffuse Gastric Cancer (HDGC) is a complex inherited syndrome caused by CDH1 germline mutations. DGC is the hallmark cancer of this genetic predisposition, but several other cancers are associated with these CDH1 mutations. In this review, we revised all studies reporting CDH1 mutations in non-GC patients. The selected studies included: (a) families aggregating with GC and other cancers, both, and (b) families presenting only non-gastric tumors association. Among non-gastric tumors, our results show that CDH1 mutations are most frequently identified in breast cancer. The frequency of missense mutations is higher in the non-GC group, as the age at diagnosis in this group. Moreover, the predominant CDH1 mutation affects the extracellular domain. Our data suggest that CDH1 genetic testing should be considered also in other cancers, especially breast tumors.

Keywords: CDH1 mutation; diffuse gastric cancer; Lobular breast cancer; hereditary cancer

1. Introduction

Hereditary Diffuse Gastric Cancer (HDGC) is a rare autosomal dominant syndrome that is associated with an increased risk of two major cancer types: diffuse gastric cancer (GC) and lobular breast cancer (LBC) [1]. In particular germline alterations of the E-cadherin gene, CDH1, occur in about 40% of all HDGC cases screened [2], with an estimated lifetime risk of diffuse gastric cancer (DGC) of 70% in men and 56% in women, and a cumulative incidence of LBC in women of around 42% [3]. The need for correct management for this inherited cancer predisposition created the International Gastric Cancer Linkage Consortium (IGCLC) in 1999 [4]. Since then, international multidisciplinary groups have been establishing and updating the clinical criteria for early disease diagnosis and for the detection of patients who should be eligible for germline CDH1 genetic screening. The more recent revised guidelines establish HDGC as any family with one of the following clinical criteria: (1) families with two or more certain cases of GC at any age, one with documented DGC; (2) personal history of DGC before the age of 40 years; (3) personal or family history of DGC and LBC, with one diagnosis before 50 years of age [2]. Although DGC is the index tumor type in HDGC, other malignant cancers [5], and congenital malformations [6], have been reported in families affected by this syndrome. For that reason, LBC, oral facial clefts,
colorectal carcinomas (CRC), and other cancers, have been suggested as suitable for \textit{CDH1} screening and early detection of HDGC \cite{2}. However, except for LBC, their inclusion in HDGC clinical definition is not yet supported due lack of robust data.

With this in mind, we have reviewed the literature for all \textit{CDH1} germline mutations in the non-DGC spectrum, as well LBC, and other epithelial cancers.

\section*{2. Methods}

We reviewed all \textit{CDH1} germline mutations reported in MEDLINE (https://www.nlm.nih.gov/medline/medline_overview.html, accessed on 12 March 2021) in individuals with diagnosed GC or other cancers, from 1998 to 2020, including original reports and literature reviews in English. The following terms were used for the literature search: E-cadherin; \textit{CDH1} gene; germline mutation; genetic screening; HDGC; IGCLC; familial GC; diffuse histotype; lobular histotype; BC; Maori kindred and prophylactic gastrectomy. This analysis was limited to studies involving subjects with HDGC, early-onset GC, and unselected GC patients screened for \textit{CDH1} germline mutations, LBC, CRC, prostate cancer (PC), ovarian cancer (OC), abdominal carcinosis (Ca), thyroid cancer (ThC), tongue cancer (ToC), in which at least one likely pathogenic, VUS or pathogenic \textit{CDH1} variant was identified. Mutation types were classified as missense, splice site, deletion, insertion, and nonsense alterations.

We considered two groups: (a) families aggregating with GC and non-GC both, and (b) families associating with other tumors.

\section*{3. Results}

Table 1 resumes \textit{CDH1} germline mutations identified in the non-GC population. Other details on the frequency of \textit{CDH1} mutations in HDGC syndrome were previously described in our recent study \cite{7}. Twenty-three families presented non-GC in their history, but only other tumor types. Instead, fifteen families aggregated with GC and other tumors, both. The mean age at diagnosis for individual \textit{CDH1} mutant carriers with GC was 40.6 years (range 21–79), and for other cancers 50.6 years (range 23–63).

\begin{table}[h]
\centering
\caption{List of \textit{CDH1} germline mutations identified in non-gastric cancers. In BC series, histotype was not reported (abbreviations: HGVS: Human Genome Variation Society nomenclature; DGC: diffuse gastric cancer; OC: other cancer; UK: United Kingdom).}
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
First Author & Country & Type & HGVS & Localization & Protein & \textit{CDH1} DGC & \textit{CDH1} OC & OCs \\
\hline
Ikonen 2001 \cite{8} & Finland & Missense & 808T>G & Ex_6 & S270A & - & 8 & PC \\
Oliveira 2002 \cite{9} & Europe & Insertion & 44dupT & Ex_1 & - & 1 & 3 & CRC(2), LBC(1) \\
Lynch 2008 \cite{10} & USA & Non sense & 70G>T & Ex_2 & - & 5 & 3 & BC \\
Xie 2011 \cite{29} & France & Non sense & 283C>T & Ex_3 & - & - & 3 & LBC \\
Chen 2013 \cite{11} & China & Missense & 1018A>G & Ex_8 & T340A & - & 3 & LBC \\
Salahshor 2001 \cite{12} & Sweden & Missense & 1774G>A & Ex_12 & A592T & - & 2 & CRC \\
Katona 2020 \cite{13} & USA & Splice site & 1566+2A>G & In_10 & - & 1 & 1 & PC \\
Gullo 2018 \cite{14} & Portugal & Missense & 1901C>T & Ex_12 & A634V & 7 & 1 & LBC \\
López 2016 \cite{15} & Spain & Deletion & 1220delC & Ex_9 & - & 2 & 1 & CRC \\
Bardram 2014 \cite{16} & Denmark & Insertion & 1565+3insTT & In_10 & - & 5 & 1 & Ca \\
More 2007 \cite{17} & Caucasian & Splice site & 49+2A>C & In_1 & - & 3 & 1 & CRC \\
 & Caucasian & Splice site & 1137G>A & Ex_8 & - & 2 & 1 & ToC \\
Kluft 2012 \cite{18} & Unknown & Non sense & 489C>A & Ex_4 & - & 2 & 1 & LBC \\
Guilford 2010 \cite{19} & Europe & Non sense & 70G>T & Ex_2 & - & 3 & 1 & BC \\
Keller 2004 \cite{20} & Germany & Deletion & 377delC & Ex_3 & - & 2 & 1 & LBC \\
Frebourg 2006 \cite{6} & Caucasian & Splice site & 531+2T>A & In_4 & - & 3 & 1 & Ca \\
\hline
\end{tabular}
\end{table}
| First Author | Country | Type               | HGVS               | Localization | Protein | CDH1_DGC | CDH1_OC | OCs  |
|--------------|---------|--------------------|--------------------|--------------|---------|----------|---------|------|
| Guilford 2010 [20] | Maori    | Splice site       | 1008G>T            | Ex_7         | -       | 9        | 1       | CRC  |
| Oliveira 2002 [9] | Pakistan | Splice site       | 832G>A             | Ex_6         | -       | 3        | 1       | LBC  |
| Lynch 2008 [10] | USA      | Non sense          | 1792C>T            | Ex_12        | -       | 1        | 1       | BC   |
| Masciari 2007 [21] | USA      | Insertion          | 517insA            | Ex_4         | -       | -        | 1       | LBC  |
| Schrader 2011 [22] | USA      | Splice site       | 1565+1G>A          | In_10        | -       | -        | 1       | BC   |
| Canada       | Missense | 8G>C               | Ex_1               | P3R          | -       | 1        | 1       | BC   |
| Canada       | Missense | 88G>A              | Ex_2               | P30T         | -       | 1        | 1       | BC   |
| Canada       | Missense | 88G>A              | Ex_2               | P30T         | -       | 1        | 1       | BC   |
| Canada       | Missense | 1223C>T            | Ex_9               | A408V        | -       | 1        | 1       | BC   |
| Canada       | Missense | 1297G>C            | Ex_9               | D433N        | -       | 1        | 1       | BC   |
| Canada       | Missense | 1813A>G            | Ex_12              | R605G        | -       | 1        | 1       | BC   |
| Canada       | Missense | 2494G>A            | Ex_16              | V832M        | -       | 1        | 1       | BC   |
| Petridis 2014 [23] | UK      | Splice site       | 48+1G>A            | Ex_1         | -       | -        | 1       | LBC  |
| UK           | Insertion | 1465insC          | Ex_10              | -            | -       | 1        | 1       | LBC  |
| UK           | Missense | 1942G>T            | Ex_13              | E648X        | -       | 1        | 1       | LBC  |
| UK           | Deletion | 2398delC           | Ex_15              | -            | -       | 1        | 1       | LBC  |
| Benusiglio 2013 [24] | France  | Splice site       | 2164+2T>A          | In_13        | -       | -        | 1       | LBC  |
| France       | Deletion | del_ex_3           | Ex_3               | -            | -       | 1        | 1       | LBC  |
| France       | Splice site | 1008+1G>A      | In_7               | -            | -       | 1        | 1       | ThC  |
| France       | Deletion | 2386delC           | Ex_15              | -            | -       | 1        | 1       | LBC  |
| Xie 2011 [25] | France   | Deletion           | 1582delC           | Ex_11        | -       | -        | 1       | LBC  |
| Manchana 2019 [26] | Thailand | Missense | 1118C>T            | Ex_8         | P373L   | -        | 1       | OC   |

### 3.1. Other Types of Cancer

We identified 54 CDH1 germline mutations in non-gastric tumors. The most frequent tumor associated with CDH1 germline mutations was BC (33/54, 61.1%), following prostate cancer (PC) (9/54, 16.7%), CRC (7/54, 12.9%), abdominal carcinosis (Ca) (2/54, 3.7%), ovarian cancer (OC) (1/54, 1.8%), thyroid cancer (ThC) (1/54, 1.8%), and tongue cancer (ToC) (1/54, 1.8%) (Figure 1). Regarding BC, interestingly we observed that in non-GC families, BC with CDH1 mutations occurs with a frequency of 42.6% (23/54), and in mixed families 18.5% (10/54). Thus, let us suppose that BC with CDH1 mutation aggregates more frequently with an independent pathway.

![Figure 1](image-url)  
Figure 1. Frequency of CDH1 germline mutations in gastric cancer and other cancers (cancers in detail are shown in the second pie).
3.2. Type of Mutations

Considering the 54 CDH1 germline mutations identified in non-GC, we verified that the frequency type of mutations were as follows: missense 48.2% (26/54), splice site 18.5% (10/54), deletion 11.1% (6/54), insertion 11.1% (6/54), and nonsense 11.1% (6/54), respectively. With regard to the localization of the mutations identified in non-GC cancers, we verified that the majority of CDH1 mutations affected the extracellular domain (31/54, 57.4%), followed by precursor (13/54, 24.1%), signal (6/54, 11.1%), cytoplasmic (3/54, 5.6%), and transmembrane (1/54, 1.8%) domains (Figure 2).

![Mutation distribution in the different sites of CDH1 gene](image)

Figure 2. Mutation distribution in the different sites of CDH1 gene (SG: signal, TM: transmembrane, red: prostate cancer, black: breast cancer, orange: ovarian cancer, blue: colorectal cancer, purple: abdominal carcinosis, green: tongue cancer, and grey: thyroid cancer).

Considering the ClinVar classification, and the submitted mutations, we identified only the S270A mutation classified as “VUS”. Most of the collected mutations were not submitted at the ClinVar platform.

4. Discussion

After lung and colorectal cancer, GC remains the third cause of cancer deaths worldwide, with about 1.2 million cases and almost one million deaths worldwide, and still is the leading cause of cancer and cancer death in selected low-income areas [27]. The substantial variations over geographic areas and declines in incidence and mortality over the last few decades indicate that most GCs have an environmental origin, Helicobacter pylori infection being by far its main cause [28]. However, there is a well identified and quantified family clustering of GC, with relative risks around two for a family history of GC in first degree relatives, after accounting for recognized environmental factors, with generally stronger associations at a younger age [29,30]. Therefore, understanding and quantifying the key components of familial and genetic factors on the different pathologic types of GC remains of key interest for understanding pathogenesis and defining early diagnosis and, hence, management. Furthermore, it might contribute to increase quality of life and the patient’s involvement in clinical decision-making [31–33].

The CDH1 gene (OMIM No. 192090) is located on chromosome 16q22.1 and encodes for the E-cadherin protein [34]. This macro-molecule is a trans- membrane glycoprotein expressed on epithelial tissue and is responsible for calcium-dependent, cell-to-cell adhesion [24]. E-cadherin protein is critical for establishing and maintaining polarized and differentiated epithelia through intercellular adhesion complexes. The human E-cadherin function is to suppress cell invasion; in fact, its deregulation is correlated with the infiltrative and metastatic ability of the tumor [23], with the consequent loss of cell adhesion and concomitant increase in cell motility [35]. In human samples, somatic CDH1 alterations are associated with poor survival and worse prognosis in gastric cancer patients [29].

In 1998, Guilford et al. identified a large family from New Zealand with multiple cases of DGC that were carriers of a causative germline mutation in the E-cadherin gene [36].
Thereafter, several publications emerged, confirming the autosomal dominant pattern of inheritance associated with germline mutations of the \textit{CDH1} gene. To date, more than 500 germline mutations have been identified in DGC families. The most common types of mutations are missense (23%), nonsense (22%), deletions (22%) or insertions (10%), and splice site (21%) [7].

In this study, firstly, we reviewed the frequency of \textit{CDH1} germline mutations in non-gastric tumors, and we identified 54 alterations. The major findings of this study were the following: (a) \textit{CDH1} germline mutations excluding GC are found predominantly BC (60% of all non-GC cancers); (b) the mean age at diagnosis was higher in the non-GC cancer (50.6 year), compared to GC (40.6 year); (c) the majority of mutations were localized in the cytoplasmic domain (Figure 2).

4.1. First Point

Recent studies demonstrated that LBC might be the first manifestation of the HDGC syndrome, even in the absence of DGC cases in the family. It was supposed that families with LBCs carrying \textit{CDH1} germline mutations cluster as independent inherited syndrome. The concept of hereditary lobular breast cancer (HLBC) is very recent [5], because some authors identified pathogenic \textit{CDH1} mutations in women with LBC [37,38], and without GC family history. To date, we do not know if asymptomatic individuals in these families will develop gastric cancer later, the cumulative risk of developing GC in these women or their relatives with \textit{CDH1} mutations is unknown; it is possible that in this contest the penetrance risk for GC is lower or absent.

In cases of the classic HDGC syndrome, individuals carrying pathogenic mutation in \textit{CDH1} have about a 70% risk of developing DGC and women have an additional LBC risk of approximately 40%, by the age of 80 years [3]. Although some authors stated that the \textit{CDH1} variant carriers lifetime risk of developing invasive BC is similar to that of \textit{BRCA} mutation carriers [39], the real risk of developing LBC in absence of a clear HDGC predisposition remains undetermined.

4.2. Second Point

BC, as well as other non-GCs associated with \textit{CDH1} mutations, could be a non-early manifestation of the complex HDGC syndrome. We observed, in fact, that the main age at diagnosis of BC, as well of other non-GCs, is higher. The pathway of \textit{CDH1} deregulation during breast and gastric carcinogenesis is different and this could explain also the different clinical manifestations. In BC, the presence of a \textit{CDH1} mutation can alter the E-cadherin function, causing a decreased cell–cell adhesion and an increased cell proliferation, so-called lobular hyperplasia. Subsequently, a second-hit \textit{CDH1} inactivation causes the loss of E-cadherin expression and, after, alters organization of the lobule. During this event, deregulated cells emerge and accumulate in the lobules creating a lobular intraepithelial neoplasia pattern. Finally, cancer cells disrupt the basement membrane and invade surrounding breast tissue, a tumor stage that is classified as invasive lobular carcinoma [5]. In \textit{CDH1} gastric carcinogenesis, the early-stage of HDGC is characterized by multiple foci of invasive (T1a) signet-ring cell (diffuse) carcinoma in the superficial gastric mucosa, with no nodal metastases. In situ signet-ring cell carcinoma and pagetoid spread of signet ring cells are recognized precursors (Tis) to T1a signet ring cell carcinoma [40]. Gastric carcinogenesis associated with \textit{CDH1} germline mutations seems more “aggressive” than LB tumorigenesis, in which missense mutations predominate. It is possible that the penetrance of cancer risk from pathogenic missense \textit{CDH1} variants is lower than that from truncating mutations, and maybe other factors (hormonal?) play a progressive synergic role with \textit{CDH1} missense mutations in BC development (as in other cancers).

4.3. Third Point

The accumulation of mutations in the cytoplasmic domain is an interesting point. The cytoplasmic domain of E-cadherin has a crucial role in its function, because it supports the
assembly of a complex of cytosolic proteins, including catenins, which provide anchorage to the actin cytoskeleton to form stable cell–cell contact [41]. Thus, the cytoplasmic domain represents a vulnerable point due to its intrinsic nature and the presence of mutations affecting this point confers a dangerous alteration of the E-cadherin protein function.

4.4. Limitations of the Study

(a) We have to consider that CDH1 gene in BC, as well in CRC, play a minor role; BRCA1/2 and mismatch repair proteins (MSH2, MSH6, MLH1, PMS2) exert a major impact in their carcinogenesis. The possibility to find a CDH1 mutation, in accord with our data, is very low in the non-GC group. At this moment, it is not clear if the identification of CDH1 mutation in the non-GC group is “casual” or associated with a possible minor pathway in non-GC tumorigenesis. We suppose that in BC the identification of CDH1 mutation is not a casual or an “incidental finding”, some data demonstrated that there is mutual exclusion of CDH1 and BRCA germline mutations in the pathway of hereditary BC [42].

(b) Another limitation of this study is the missing information about ClinVar classification. Unfortunately, not all mutations were submitted at the ClinVar platform, and this work should be completed to better clarify the potential pathogenic role of CDH1 mutations reported in the current study.

(c) The motivation to perform CDH1 genetic screening in such populations, without apparent indications, is unknown. Unfortunately, the authors did not clarify this point. This missing information represents another limitation of this study.

5. Conclusions

In conclusion, in comparison with our previous study [7], our results suggest that about 7% of the overall CDH1 mutations are present in non-gastric tumors. The majority of mutations are identified in BC, and the age at diagnosis is higher in other cancers, in comparison to GC group. It is plausible that non-GC cancers are a late manifestation of the HDGC syndrome. Mutations affect predominantly the cytoplasmatic domain of CDH1 gene, a vulnerable place that exerts a pivotal role in the cell–cell adhesion and polarization. CDH1 missense mutations are more frequent in non-gastric tumors (48.2%), and other factors could play a synergistic role with missense mutations in the development of non-GCs. At this moment, the value of CDH1 testing in non-GC cancers other than BC may not be high, given the paucity of evidence. A prospective study may be of more value in changing clinical practice.

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References
1. Corso, G.; Montagna, G.; Figueiredo, J.; La Vecchia, C.; Fumagalli Romario, U.; Fernandes, M.S.; Seixas, S.; Roviello, F.; Trovato, C.; Guerini-Rocco, E.; et al. Hereditary Gastric and Breast Cancer Syndromes Related to CDH1 Germline Mutation: A Multidisciplinary Clinical Review. Cancers 2020, 12, 1598. [CrossRef]
2. Blair, V.R.; McLeod, M.; Carneiro, F.; Coit, D.G.; D’Addario, J.L.; van Dieren, J.M.; Harris, K.L.; Hoogerbrugge, N.; Oliveira, C.; van der Post, R.S.; et al. Hereditary diffuse gastric cancer: Updated clinical practice guidelines. Lancet Oncol. 2020, 21, 386–397. [CrossRef]
3. Hansford, S.; Kaurah, P.; Li-Chang, H.; Woo, M.; Senz, J.; Pinheiro, H.; Schrader, K.A.; Schaeffer, D.F.; Shumansky, K.; Zogopoulos, G.; et al. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. JAMA Oncol. 2015, 1, 23–32. [CrossRef]
4. Caldas, C.; Carneiro, F.; Lynch, H.T.; Yokota, J.; Wiesner, G.L.; Powell, S.M.; Lewis, F.R.; Huntsman, D.G.; Pharoah, P.D.; Jankowski, J.A.; et al. Familial gastric cancer: Overview and guidelines for management. J. Med. Genet. 1999, 36, 873–880.

5. Corso, G.; Figueiredo, J.; La Vecchia, C.; Veronesi, P.; Pravettoni, G.; Macis, D.; Karam, R.; Lo Gullo, R.; Provenzano, E.; Toesca, A.; et al. Hereditary lobular breast cancer with an emphasis on E-cadherin genetic defect. J. Med. Genet. 2018, 55, 431–441. [CrossRef]

6. Frebourg, T.; Oliveira, C.; Hoehn, P.; Karam, R.; Manouvrier, S.; Graziano, F.; Bignon, Y.J. Germline mutations of the E-cadherin gene in Women with breast cancer. J. Med. Genet. 2006, 43, 138–142. [CrossRef]

7. Corso, G.; Corso, F.; Bellerba, F.; Carneiro, P.; Seixas, F.; Cioffi, A.; La Vecchia, C.; Magnoni, F.; Bonanni, B.; Veronesi, P.; et al. Geographical Distribution of E-cadherin Germline Mutations in the Context of Diffuse Gastric Cancer: A Systematic Review. Cancers 2021, 13, 1269. [CrossRef]

8. Ikonen, T.; Matikainen, M.; Mononen, N.; Hyytinen, E.; Helin, H.; Tommola, S.; Tammela, T.; Pukkala, E.; Schleutker, J.; Kallioniemi, O.; et al. Association of E-cadherin germline alterations with prostate cancer. Clin. Cancer Res. 2001, 7, 3465–3471.

9. Oliveira, C.; Bordin, M.C.; Grehan, N.; Huntsman, D.; Suriano, G.; Machado, J.C.; Kiviluoto, T.; Aaltonen, L.; Jackson, C.E.; Seruca, R.; et al. Screening E-cadherin in gastric cancer families reveals germline mutations only in hereditary diffuse gastric cancer kindred. Hum. Mutat. 2002, 19, 510–517. [CrossRef]

10. Lynch, H.T.; Kaurah, P.; Wirtzfeld, H.; Ruzzo, A.; Tung, N.; Pinto-Ribeiro, I.; et al. Phenotypic heterogeneity of hereditary diffuse gastric cancer: Report of a family with early-onset disease. Gastrointest. Endosc. 2018, 87, 1566–1575. [CrossRef]

11. Lopez, M.; Cervera-Acedo, C.; Santibañez, P.; Salazar, R.; Sola, J.J.; Dominguez-Garrido, E. A novel mutation in the CDH1 gene in a Spanish family with hereditary diffuse gastric cancer. Springerplus 2016, 5, 1181. [CrossRef]

12. Salahshor, S.; Haixia, H.; Hu, H.; Kristensen, V.; Loman, N.; Sjöberg-Margolin, S.; Borg, A.; Børresen-Dale, A.; Vorechovsky, I.; Lindblom, A. Low frequency of E-cadherin alterations in familial breast cancer. Breast Cancer Res. 2001, 3, 199–207. [CrossRef]

13. Katona, B.W.; Clark, D.F.; Domchek, S. CDH1 on Multigene Panel Testing: Look Before You Leap. J. Natl. Cancer Inst. 2020, 112, 330–334. [CrossRef]

14. Gullo, I.; Devezas, V.; Baptista, M.; Garrido, L.; Castedo, S.; Morais, R.; Wen, X.; Rios, E.; Pinheiro, J.; Pinto-Ribeiro, I.; et al. Germline mutations in Chinese gastric cancer patients. J. Med. Genet. 2013, 41, 138–142. [CrossRef] [PubMed]

15. Manchana, T.; Phowthongkum, P.; Peerapakpinno, C. Germline mutations in Thai patients with nonmucinous epithelial ovarian cancer. World J. Clin. Oncol. 2019, 10, 358–368. [CrossRef] [PubMed]

16. Bardram, L.; Hansen, T.V.; Gerdes, A.M.; Timshel, S.; Friis-Hansen, L.; Federspiel, B. Prophylactic total gastrectomy in hereditary diffuse gastric cancer: Identification of two novel CDH1 gene mutations—A clinical observational study. Fam. Cancer 2014, 13, 231–242. [CrossRef] [PubMed]

17. More, H.; Humar, B.; Weber, W.; Ward, R.; Christian, A.; Lintott, C.; Graziano, F.; Ruzzo, A.M.; Acosta, E.; Boman, B.; et al. Identification of seven novel germline mutations in the human E-cadherin (CDH1) gene. Hum. Mutat. 2007, 28, 203. [CrossRef]

18. Kluijtm, I.; Siemerink, E.J.; Ausems, M.G.; van Os, T.A.; de Jong, D.; Simões-Correa, J.; van Krieken, J.H.; Lichtenberg, M.J.; Figueiredo, J.; van Riel, E.; et al. CDH1-related hereditary diffuse gastric cancer syndrome: Clinical variations and implications for counseling. Int. J. Cancer 2012, 131, 367–376. [CrossRef]

19. Guilford, P.; Humar, B.; Blair, V. Hereditary diffuse gastric cancer: Translation of CDH1 germline mutations into clinical practice. Gastric Cancer 2010, 13, 1–10. [CrossRef]

20. Keller, G.; Vogelsang, H.; Becker, I.; Plaschke, S.; Ott, K.; Suriano, G.; Mateus, A.R.; Seruca, R.; Biedermann, K.; Huntsman, D.; et al. Germline mutations of the E-cadherin (CDH1) and TP53 genes, rather than of RUNX3 and HPP1, contribute to genetic predisposition in German gastric cancer patients. J. Med. Genet. 2004, 41, e89. [CrossRef]

21. Masciari, S.; Larsson, N.; Senz, J.; Boyd, N.; Kaurah, P.; Kandel, M.; Harris, L.; Pinheiro, H.; Troussard, A.; Miron, P.; et al. Germline E-cadherin mutations in familial lobular breast cancer. J. Med. Genet. 2007, 44, 726–731. [CrossRef]

22. Schrader, K.; Masciari, S.; Boyd, N.; Salamanca, C.; Senz, J.; Saunders, D.; Yorida, E.; Maines-Bandiera, S.; Kaurah, P.; Tung, N.; et al. Germline mutations in CDH1 are infrequent in women with early-onset or familial lobular breast cancers. J. Med. Genet. 2011, 48, 64–68. [CrossRef]

23. Takeichi, M. Cadherins in cancer: Implications for invasion and metastasis. Curr. Opin. Cell Biol. 1993, 5, 806–811. [CrossRef]

24. Takeichi, M. Cadherin cell adhesion receptors as a morphogenetic regulator. Science 1991, 251, 1451–1455. [CrossRef] [PubMed]

25. Xie, Z.; Li, L.; Laquet, C.; Renault-Lorca, F.; Uhrhammer, N.; Xie, X.M.; Bignon, Y.J. Germline mutations of the E-cadherin gene in families with inherited invasive lobular breast carcinoma but no diffuse gastric cancer. Cancer 2011, 117, 3112–3117. [CrossRef]

26. Mamanaka, T.; Phowthongkum, P.; Peerapakpinno, C. Germline mutations in Thai patients with nonmucinous epithelial ovarian cancer. World J. Clin. Oncol. 2019, 10, 358–368. [CrossRef] [PubMed]
30. Yaghoobi, M.; McNabb-Baltar, J.; Bijarchi, R.; Hunt, R. What is the quantitative risk of gastric cancer in the first-degree relatives of patients? A meta-analysis. *World J. Gastroenterol.* 2017, 23, 2435–2442. [CrossRef]

31. Gorini, A.; Miglioretti, M.; Pravettoni, G. A new perspective on blame culture: An experimental study. *J. Eval. Clin. Pract.* 2012, 18, 671–675. [CrossRef]

32. Oliveri, S.; Ferrari, F.; Manfrinati, A.; Pravettoni, G. A systematic review of the psychological implications of genetic testing: A comparative analysis among cardiovascular, neurodegenerative and cancer diseases. *Front. Genet.* 2018, 9, 624. [CrossRef] [PubMed]

33. Masiero, M.; Riva, S.; Fioretti, C.; Pravettoni, G. Pediatric blood cancer survivors and tobacco use across adolescence and emerging adulthood: A narrative review. *Front. Psychol.* 2016, 7, 392. [CrossRef]

34. Berx, G.; Cleton-Jansen, A.M.; Nollet, F.; de Leeuw, W.J.; Van de Vijver, M.; Cornelisse, C. E-cadherin is a tumour/invasion suppressor gene mutated in human lobular breast cancers. *EMBO J.* 1995, 14, 6107–6115. [CrossRef] [PubMed]

35. Christofori, G.; Semb, H. The role of the cell-adhesion molecule E-cadherin as a tumour-suppressor gene. *Trends Biochem. Sci.* 1999, 24, 73–76. [CrossRef]

36. Guilford, P.; Hopkins, J.; Harraway, J.; McLeod, M.; McLeod, N.; Harawira, P.; Taite, H.; Scoular, R.; Miller, A.; Reeve, A.E. E-cadherin germline mutations in familial gastric cancer. *Nature* 1998, 392, 402–405. [CrossRef]

37. Benusiglio, P.R.; Malka, D.; Rouleau, E.; De Pauw, A.; Buecher, B.; Noguès, C.; Fourme, E.; Colas, C.; Coulet, F.; Warcoin, M.; et al. CDH1 germline mutations and the hereditary diffuse gastric and lobular breast cancer syndrome: A multicentre study. *J. Med. Genet.* 2013, 50, 486–489. [CrossRef]

38. Petridis, C.; Shinomiya, I.; Kohut, K.; Gorman, P.; Caneppele, M.; Shah, V.; Troy, M.; Pinder, S.E.; Hanby, A.; Tomlinson, P.M.; et al. Germline CDH1 mutations in bilateral lobular carcinoma in situ. *Br. J. Cancer* 2014, 110, 1053–1057. [CrossRef] [PubMed]

39. Gamble, C.; Havrilisky, L.; Myers, E.; Chino, J.; Hollenbeck, S.; Plchta, J.; Marcom, P.; Hwang, E.; Kauff, N.; Greenup, R. Cost Effectiveness of Risk-Reducing Mastectomy versus Surveillance in BRCA Mutation Carriers with a History of Ovarian Cancer. *Ann. Surg. Oncol.* 2017, 24, 3116–3123. [CrossRef]

40. Carneiro, F.; Huntsman, D.G.; Smyrk, T.; Owen, D.; Seruca, R.; Pharoah, P.; Caldas, C.; Sobrinho-Simões, M. Model of the early development of diffuse gastric cancer in E-cadherin mutation carriers and its implications for patient screening. *J. Pathol.* 2004, 203, 681–687. [CrossRef]

41. Melo, S.; Figueiredo, J.; Fernandes, M.; Gonçalves, M.; Morais-de-Sá, E.; Sanches, J.; Seruca, R. Predicting the Functional Impact of CDH1 Missense Mutations in Hereditary Diffuse Gastric Cancer. *Int. J. Mol. Sci.* 2017, 18, 2687. [CrossRef] [PubMed]

42. Corso, G. Mutual exclusion of CDH1 and BRCA germline mutations in the pathway of hereditary breast cancer. *Arch. Gynecol. Obstet.* 2018, 297, 1067–1068. [CrossRef] [PubMed]