Hereditary diffuse gastric cancer: association with lobular breast cancer

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Abstract Hereditary diffuse gastric cancer (HDGC) has been shown to be caused by germline mutations in the gene CDH1 located at 16q22.1, which encodes the cell–cell adhesion molecule, E-cadherin. Not only does loss of expression of E-cadherin account for the morphologic differences between intestinal and diffuse gastric cancer (DGC) variants, but it also appears to lead to distinct cellular features which appear to be common amongst related cancers that have been seen in the syndrome. As in most hereditary cancer syndromes, multiple organ sites may be commonly affected by cancer, in HDGC, lobular carcinoma of the breast (LBC) and possibly other organ sites have been shown to be associated with the familial cancer syndrome. Given the complexity of HDGC, not only with regard to the management of the DGC risk, but also with regard to the risk for other related cancers, such as LBC, a multi-disciplinary approach is needed for the management of individuals with known CDH1 mutations.

Keywords Hereditary diffuse gastric cancer (HDGC) · Diffuse gastric cancer · E-cadherin mutation · CDH1 mutation · Lobular breast cancer · Screening · Prophylactic total gastrectomy

Abbreviations DGC diffuse gastric cancer GC gastric cancer HDGC hereditary diffuse gastric cancer LBC lobular breast cancer

Introduction

Despite an overall decrease in the global incidence of gastric cancer (GC) [1], the incidence of the subtype, diffuse gastric cancer (DGC) has remained stable and may even be increasing [2]. Within the past ten years, germline mutations in CDH1, which encodes E-cadherin, have been found [3] in over 50% of hereditary diffuse gastric cancer (HDGC) families with at least two cases of GC, with one diagnosed as DGC before the age of 50 years [4]. Within these HDGC families, we and others have noted an over-representation of lobular breast cancer (LBC) [4–8]. This observation has led to efforts to determine whether or not CDH1 is a breast cancer susceptibility gene, distinct from...
its gastric cancer risk. Recently our group has reported a novel germline CDH1 truncating mutation (517insA) in an LBC family with no known history of GC [9]. Within this review we report a germline CDH1 mutation in a second family in which breast cancer is the predominant cancer diagnosis. The management of HDGC in all patients with a particular focus on the management of the breast cancer risk associated with germline CDH1 mutations will be discussed.

Methods

The described family was referred to the ongoing HDGC study at the British Columbia Cancer Agency from a cancer genetics clinic in Seattle, WA, USA. Informed consent was obtained from the proband by the referring genetic counselor following ascertainment of a detailed cancer family history and appropriate genetic counseling prior to germline mutation testing. Our laboratory carried out the molecular genetic testing for the CDH1 mutation on a research basis. Approval for the HDGC study is by the clinical research ethics board of the University of British Columbia.

The proband (IV-4) was diagnosed with widely metastatic lobular breast cancer at age 53 years (Fig. 1a). Her family, of European ancestry, had a history of breast cancer diagnoses occurring in an autosomal dominant fashion on the maternal side of the family where her mother, aunt, and first cousin developed breast cancer in their 50’s. Due to her high-risk pedigree BRCA1, BRCA2, and PTEN genetic testing was undertaken and all were negative. CDH1 testing was also pursued.

Results

All 16 exons were amplified for DHPLC analysis [6]. For exon 10 of CDH1, the initial amplicon failed and was therefore analyzed by direct sequencing and thus revealed a donor splice site mutation, 1565 + 1G > A (Fig. 1b). Due to its position at a donor splice site, this mutation is regarded as pathogenic [10].

The proband’s sisters (IV-2 and IV-6) participated in all aspects of the proband’s genetic consultation. They were appropriately concerned about their risk of breast cancer, but had not thought much about the possibility of getting gastric cancer until the CDH1 mutation was found. IV-2 and IV-6 had predictive genetic testing for the CDH1 mutation testing and both were found to be negative. Other family members are being informed about the availability of predictive genetic testing.

Fig. 1 (a) Pedigree of family reported showing a predominance of breast cancer. (b) Sequence from family carrying 1565 + 1G→A mutation
Discussion

E-cadherin

*CDH1* (OMIM *192090)*, located on chromosome 16q22.1 encodes, E-cadherin, an epithelial transmembrane cell–cell adhesion molecule and member of the cadherin superfamily of glycoproteins. In a zipper-like fashion, its extracellular domain forms calcium-dependent homodimers between the E-cadherin molecules of adjacent epithelial cells, to act as the primary mediator of epithelial cell adhesion at the adherens junction complex [11]. Through interactions of its cytoplasmic tail with multiple signalling and structural molecules, such as the catenins, E-cadherin, maintains cellular adhesion and epithelial architecture with this link to the cytoskeleton. The cytoplasmic tail of E-cadherin directly associates with $\beta$-catenin and $\gamma$-catenin which in turn binds to the $\alpha$-actin microfilaments of the cytoskeleton, directly or through $\alpha$-catenin [12]. p120-catenin also associates with E-cadherin’s cytoplasmic tail at a different site, the juxtamembrane domain, and acts to both strengthen the adhesion between cells and regulate cadherin membrane trafficking and degradation [13, 14]. E-cadherin is considered to have an invasion suppressor role, where decreased expression permits cells to dissociate from each other in order to migrate and invade [15]. In cancers, this manifests as increased infiltrative and metastatic potential [16]. E-cadherin is also thought to act as a tumour suppressor, potentially through its interaction with the multipurpose $\beta$-catenin molecule which is an effector of the WNT signalling pathway [17]. Loss of E-cadherin can result in $\beta$-catenin release from the membrane and translocation to the nucleus where it complexes with Tcf/Lef-1 transcription factors to initiate transcription of WNT responsive genes [18]. Activation of these genes have been implicated in tumourigenesis through the WNT signalling pathway as seen in adenomatous polyposis coli (APC) [19]. In support of the role of E-cadherin as a tumour suppressor is the observation of abnormal or absent E-cadherin expression in precursor lesions of DGC and LBC, where the phenomenon is seen in in situ signet ring cell carcinomas found in prophylactic gastrectomy specimens from germline *CDH1* mutation carriers [20] and the lobular carcinoma in situ lesions seen adjacent to invasive lobular breast cancers [21]. These examples suggest that loss of E-cadherin is an early or even tumour-initiating event, however the actual molecular basis of such a potential role of E-cadherin in such cases is unknown.

Inactivating *CDH1* mutations are found in 50% of sporadic DGCs [22, 23] and cluster between exons seven and nine [11], in contrast with the low percentage of mutations seen in sporadic intestinal type GCs [23]. Decreased expression of E-cadherin in DGCs may account for morphologic differences between intestinal and DGC variants [24]. Unlike somatic *CDH1* mutations, germline mutations associated with DGC are distributed throughout the gene [7] (Fig. 2). In the cancers from individuals with *CDH1* mutations, *CDH1* acts as a classic tumour suppressor gene with loss of expression of the wildtype allele [25, 26]. In a single study of 6 hereditary DGC cancers, inactivation of the wild-type allele could be attributed to promoter hypermethylation in 5 (83%) of cases [26]. This finding warrants verification in a larger cohort as abnormal promoter methylation in early cancers could potentially form the basis of a screening test.

![Legend: missense mutation](#) splice site mutation (nonsense and other truncating mutations)

**Fig. 2** DGC and LBC associated *CDH1* germline mutations. Mutations shown above *CDH1* gene schematic occur in families with DGC history and those below *CDH1* occur in families with an additional or exclusive LBC history. In addition to the known *CDH1* germline mutations compiled by Kaurah et al. [4], the recent mutation in an LBC family [9] and novel mutation from this paper are shown and identified below the symbol denoting mutation type. * Denotes the halfway point of the *CDH1* coding sequence (1324 or the start of exon 10).
Lobular breast cancer and diffuse gastric cancer: loss of E-cadherin

Currently germline mutations in single genes account for approximately 5–10% of breast cancer [27]. High penetrance genes such as BRCA1 and 2 account for 3–8%, and TP53 and PTEN as seen in Li-Fraumeni and Cowden syndrome together only account for <0.1% of breast cancer diagnoses [28]. Other medium and low penetrance genes such as CHK2, BRIP1, PALB2 and ATM [29–32] have been identified, however, there still remains a proportion of hereditary breast cancer not yet determined. LBC accounts for approximately 10% of all breast cancers compared to the other major histologic subtype, invasive ductal carcinoma (IDC) [33]. Several factors suggest that LBC has a stronger hereditary basis relative to IDC, such as the higher frequency of bilateral disease [33], and also where excess familiaity of LBC has been observed in population studies [34]. LBCs compose only 3% and 9% of the breast cancer tumour types seen in germline BRCA 1 and 2 mutation carriers, respectively [35], illustrating that the genetic risk factors for the majority of cases are unaccounted for by these genes.

The histology of LBC is characterized by infiltrative cancer cells which are isolated, highly dispersive and demonstrate a growth pattern with scattered and single files of tumor cells dispersed in stromal tissue [36]. This pathologic appearance is remarkably similar to DGCs and both LBC and DGC demonstrate characteristic mucinous, signet ring cells. This is not unexpected as E-cadherin staining is absent in 85% of sporadic invasive LBC [37] and somatic CDH1 mutations have been identified in 56% of sporadic LBCs [38]. Furthermore, in IDC, somatic CDH1 mutations are not found [38] and complete loss of E-cadherin expression is an uncommon feature. As loss of E-cadherin expression is a distinctive trait of both LBCs and DGCs, it likely contributes to the unique histopathologic features shared by the two cancers.

There are some differences with regard to the nature of the mutations seen in LBC and DGC. Generally mutations associated with sporadic LBC have been found to be nonsense or frameshift mutations [39] which encode truncated, non-functional proteins, whereas in sporadic DGC, mutations have generally been found to be splice site and in-frame mutations [11]. In sporadic LBC, mutations in CDH1 are spread throughout the gene [11] compared with the mutations seen in sporadic DGC which tend to cluster. Germline CDH1 mutations associated with DGC and/or LBC occur throughout the gene (Fig. 2). However, when the DGC and LBC associated CDH1 mutations are tabulated and compared based on their 3' or 5' positions relative to the halfway point of the CDH1 coding sequence (1324 or the start of exon 10), LBC associated mutations show a statistically significant trend towards clustering at the 3' end (Fisher’s exact test, two-tailed P-value equals 0.0467) (Fig. 2). As this association is of weak statistical significance, it is unlikely to impact clinical testing strategies. Future analyses of novel germline LBC-associated CDH1 mutations should help to confirm this observation. Another difference between the molecular genetics of the two types of cancers, is that in sporadic LBC, silencing of E-cadherin expression is generally accomplished by a mutation in one allele in combination with loss of heterozygosity (LOH) or promoter hypermethylation in the remaining allele [40]. This is in contrast to sporadic DGC, where biallelic inactivation is achieved by mutations in one allele in concert with promoter hypermethylation in the other [41].

We have recently identified a truncating germline CDH1 mutation in an LBC family where analysis of the tumour was suggestive of partial LOH in the WT allele [9]. Our current case demonstrates a germline CDH1 mutation (1565 + 1G > A) in a predominantly breast cancer family, which is predicted to disrupt splicing. The mutation is in the same conserved position as a previously reported mutation (1565 + 1G > T) which was found in an Arabian HDGC family with no recorded history of breast cancer [42]. Moreover, a previous study reported a germline missense mutation in a proband with LBC but did not detail family history, or functionally characterize the missense mutation [43]. These examples demonstrate the need for further studies of germline mutations in LBC families in order to determine the mutation frequency and potential genotype-phenotype correlations.

Lobular breast cancer and HDGC

Breast cancer has been observed in HDGC kindreds to the extent where clustering of LBCs within HDGC families has led to the misclassification of families as breast cancer kindreds who test negative for BRCA1/2 mutations [4]. In 1998, Keller described the first case of histologically defined LBC in association with HDGC [5]. Since then, several more HDGC families with associated breast cancer were reported where it was observed, that these cases were LBCs when pathology was available [4, 6–8]. Prior to establishment of the association between HDGC and LBC, several efforts to determine whether CDH1 was a breast cancer susceptibility gene were attempted in view of the well-recognised phenotype of loss of E-cadherin expression displayed by the breast cancer subtype. For various reasons these studies failed to demonstrate the link. Rahman et al. examined 65 cases of lobular carcinoma in situ, however did not pre-screen the cases based on family history and included a wide age range, from 26 to
71 years, not necessarily in keeping with the usual age of onset seen in hereditary cancer syndromes [44]. Salashor examined 19 breast cancer tumours exhibiting LOH at the CDH1 locus, however of those, only 3 were confirmed to be pure LBC or mixed LBC/IDC pathology [45]. Lei examined 13 familial LBC cases and found no mutations, however did not define the extent of the family history [46].

Penetrance data based on 11 HDGC families, estimated the cumulative risk for LBC for female mutation carriers to be 39% (95% CI, 12–84%) by 80 years of age [47]. More recently we have published an estimated cumulative risk for breast cancer for females by the age of 75 years as being 52% (95% CI, 29–94%) from analysis of 4 predominantly gastric cancer pedigrees from Newfoundland with the 2398delC CDH1 founder mutation [4]. This is with the caveat that LBC risk for CDH1 mutation carriers has been assessed within high risk HDGC families, leading to a potential ascertainment bias and underestimation of the role of CDH1 mutations in LBC development. To accommodate for this we have begun analysis of CDH1 mutations within familial lobular breast cancer families or those families ascertained through a relatively young index case with confirmed LBC and have found germline CDH1 mutations in these kindreds [9].

Clinical implications of CDH1 associated LBC risk

At this time, it seems reasonable to conclude that at least four groups of women are at increased risk for LBC: women with LBC and a family history of breast cancer, women with a known CDH1 mutation, women from families with diffuse gastric cancer in whom no CDH1 mutation has yet been identified; and women with a germline BRCA2 mutation. Since there has not yet been a large population based study of the prevalence of CDH1 mutations among women with lobular breast cancer, it is premature to recommend genetic evaluation to women with a family history of breast cancer unless, at the very least, one of the breast cancers can be shown to have been lobular. Additional research can be expected to provide better guidance for these families.

Although there are not yet definitive data available on surveillance or risk reduction programs for women with known CDH1 mutations or untested women from CDH1-positive families, the high lifetime risk of LBC (39–52%) [4, 47] that these women face mandates their careful management. We suggest that they follow the recommendations for other high-risk women with hereditary breast cancer predisposition. This subgroup should be advised to practice breast self-examination; and to have annual mammograms, and semiannual clinical breast examination, beginning at least by age 30. There is certainly interest in regular bilateral breast MRI, as lobular breast cancer are known to frequently elude mammographic detection because they do not form masses or develop calcifications. These women can also be counseled to consider hormonal chemoprevention, since most LBCs are estrogen receptor positive [33], and both tamoxifen and raloxifene reduce the risk of estrogen receptor positive [48, 49] breast cancers in randomized trials. In addition, the risk reduction was greatest with both agents in women with lobular carcinoma in situ [50].

Prophylactic mastectomy may also be considered an option by some CDH1-positive women, particularly those who have been previously diagnosed with breast cancer in one breast or those who have had to undergo multiple biopsies for abnormal clinical findings. Several studies have reported a 90% reduction in breast cancer incidence with prophylactic mastectomy among women with a strong family history or with a germline BRCA1 or BRCA2 mutation [51, 52]. The published series include some lobular breast cancers, but not at numbers sufficient to permit meaningful subset analysis at this time.

Management of hereditary diffuse gastric cancer

Penetrance studies examining data from HDGC families, have estimated the lifetime risk of developing gastric cancer by age 75 and 80 respectively, to be from 40–67% in men, to 63–83% in women [4, 47]. Although identification of germline CDH1 mutations has enabled a significant proportion of HDGC families to utilise predictive testing to determine their individual risks of GC within CDH1 mutation positive pedigrees, unfortunately screening for DGC is ineffective and the current recommendation is for consideration of prophylactic gastrectomy in mutation positive individuals. Positron emission tomography [53] and chromoendoscopic-directed biopsies [54] have been proposed over basic endoscopy as more sensitive means of screening carriers, however screening methods have been consistently undermined by the recurrent discovery of multifocal DGC lesions underlying normal mucosa in prophylactic gastrectomy specimens of individuals with recent negative screening [4, 55, 56]. Regardless of the current limitations of screening, it is currently recommended that consideration for genetic testing and screening begin in at risk individuals in the late teens or early twenties [4] and that prophylactic total gastrectomy be considered in the early twenties for mutation carriers. Female mutation carriers will need specialized counseling to the potential nutritional effects on pregnancy following gastrectomy [57]. Further studies are currently underway to examine the quality of life impact of
prophylactic gastrectomies. In the case report herein, although there was a GC in the maternal grandfather, the family history was more striking for the large number of breast cancer cases. This highlights the particular challenges we currently face with regard to counseling these families which appear to be mainly breast cancer, as it is unknown if the penetrance of DGC in this family is as high as it is in other HDGC pedigrees.

**Conclusion**

HDGC is one of a number of hereditary cancer syndromes that feature both an increased breast and gastric cancer risk (Table 1). In general, a lack of shared genetic risks for most breast and GI cancers was suggested through a recent study of 13,023 genes in 11 breast and 11 colon cancer cell lines in which the only commonly mutated gene between these two cancer types is p53 [58]. This likely reflects underlying differences in the biology of these diseases, however also highlights the unique nature of germline mutations in the CDH1 gene which are strongly associated with specific histologically defined subtypes of breast and GI cancer, namely LBC and DGC which are both part of the HDGC syndrome.

With the recent demonstration of a CDH1 mutation in a family ascertained through an index case of LBC and in view of the additional new mutation in a predominantly breast cancer family that we have described here, the evidence for establishing LBC as part of the HDGC syndrome is strong. There now is a need for establishing the prevalence of CDH1 mutations in LBC families to avoid the ascertainment bias generated from only looking at cases from families identified because of their family history of GC. It is not currently known what the risk of GC is in these families which present predominantly as having a susceptibility to breast cancer and therefore identification of CDH1 as a true susceptibility gene for LBC could result in CDH1 screening and effective risk reduction strategies for selected breast cancer families and further studies examining their risk for gastric and other cancers.

Most hereditary cancer syndromes are associated with cancer risk involving multiple organs. Here we have discussed germline CDH1 mutations and the risks with regard to DGC and LBC, however as the recognised spectrum of related cancers broadens, more affected families will be identified and successfully managed with regard to avoidance of specific cancer risks. Longer life expectancy in individuals with penetrant mutations could potentially lead to the development of different, later onset disease as yet to be identified in these kindreds. This represents a particular challenge in hereditary cancer practice as the clinical community tends to be segregated into organ

| Syndrome | Evidence for association with the syndrome |
|----------|------------------------------------------|
| **BRCA2 Hereditary Breast/Ovarian Cancer** | AD | Breast | 0.75 | Ovary | 0.75 | Prostate | 0.75 |
| **BRCA1 Hereditary Breast/Ovarian Cancer** | AD | Breast | 0.75 | Ovary | 0.75 | Prostate | 0.75 |
| **Peutz-Jeghers Syndrome** | AD | Gastrointestinal (GI) tract | 0.75 | STK 11 | 0.75 |

Table 1 Other syndromes with familial susceptibility to breast and gastric cancers

- **BRCA2 Hereditary Breast/Ovarian Cancer**: BC is considered an integral tumor of the syndrome with an average cumulative risk in carriers by age 70 years of 4.5% (95% confidence interval 3.1–5.6%) [59].
- **BRCA1 Hereditary Breast/Ovarian Cancer**: BC is considered an integral tumor of the syndrome with an average cumulative risk in carriers by age 70 years of 7.2% (95% confidence interval 6.7–9%) [60].
- **Peutz-Jeghers Syndrome**: GI tract cancer risk is 0.75 times that of the general population [61].
| Syndrome                                      | Mode of inheritance | Associated gene(s) | Sites of primary cancer(s) | Evidence for association with the syndrome |
|----------------------------------------------|---------------------|--------------------|---------------------------|------------------------------------------|
| Cowden Syndrome                              | AD                  | PTEN               | Breast, Thyroid, Endometrium | BC is considered an integral tumor of the syndrome with an incidence of 22–50% [66, 67] |
|                                              |                     |                    |                            | GC in situ has been reported in a patient with Cowden Syndrome [68] |
| Li-Fraumeni Syndrome                         | AD                  | TP53, CHK2         | Breast, Adrenal cortex, Kidney, Pancreas | BC is frequently found in families with this cancer susceptibility syndrome [69] |
|                                              |                     |                    |                            | Chompret expanded the spectrum of cancers to include GC [70] |
|                                              |                     |                    |                            | Germline TP53 mutations have been found in GC families without CDH1 mutations [71–73] |
|                                              |                     |                    |                            | The 1100delC CHK2 allele confers a 2.2 fold risk of BC to carriers [29], however germline mutations in GC kindreds have not been identified [74] |
| Familial Adenomatous Polyposis               | AD                  | APC                | Colon and rectum, Duodenum, Thyroid, Pancreas | Literature review by Shimoyama et al. totalled 30 reported cases of GC and FAP [76] |
|                                              |                     |                    |                            | 47% to 49% of primary BCs had promoter hypermethylation at the APC locus [77, 78] |
|                                              |                     |                    |                            | 23% of LBCs have been shown to have LOH of APC [43] |
| Lynch Syndrome (Hereditary Nonpolyposis Colon Cancer (HNPCC)) | AD                  | hMLH1, hMSH2, hMSH6, hPMS1, hPMS2 | Colon and rectum, Endometrium, Stomach, Small intestine, Urothelium, Kidney, Ovary, Skin, Pancreas, Brain, White blood cells | Gastric cancer accounted for 5% of cancers in families harboring MLH1 or MSH2 mutations [76] |
|                                              |                     |                    |                            | hMLH1 mutations in large kindred segregated with BCs exhibiting microsatellite instability (MSI) [79] |
|                                              |                     |                    |                            | A slight increased incidence of BC was seen in hMLH1 mutation carriers [80] |
|                                              |                     |                    |                            | Germline hMSH2 mutation carrier with BC exhibited LOH for hMSH2 in tumors analyzed [81] |
|                                              |                     |                    |                            | Analysis of primary invasive BCs demonstrated that 25% of tumours were immunonegative for MSH2 staining [82] |
| Ataxia-telangiectasia (AT)                   | AR                  | ATM                | White blood cells | Mutations causing AT in homozygotes, confer susceptibility to BC in heterozygotes, where women with ATM mutations have a ~2-fold risk of BC and ~15% of these women will develop the disease [32] |
|                                              |                     |                    |                            | GC has been reported in association with the syndrome [83–85] |
|                                              |                     |                    |                            | There is evidence of excess risks of GC in heterozygotes (RR = 3.39, 95% CI = 0.86 to 13.4) [86] |
specific specialties where as the cancer risks and the risk reduction strategies for germline mutation carriers require a variety of expertise. The medical needs of the HDGC families are therefore best served through an engaged multidisciplinary team.

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References

1. Crew KD, Neugut AI (2006) Epidemiology of gastric cancer. World J Gastroenterol 3:354–362
2. Henson DE, Dittus C, Younes M et al (2004) Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973–2000: increase in the signet ring cell type. Arch Pathol Lab Med 7:765–770
3. Guilford P, Hopkins J, Harraway J et al (1998) E-cadherin germline mutations in familial gastric cancer. Nature 6674:402–405
4. Kaurah P, MacMillan A., Boyd N et al (2007) Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. JAMA 21:2360–2372
5. Keller G, Vogelsang H, Becker I et al (1999) Diffuse type gastric and lobular breast carcinoma in a familial gastric cancer patient with an E-cadherin germline mutation. Am J Pathol 2:337–342
6. Suriano G, Yew S, Ferreira P et al (2005) Characterization of a recurrent germ line mutation of the E-cadherin gene: implications for genetic testing and clinical management. Clin Cancer Res 15:5401–5409
7. Oliveira C, Bordin MC, Grehan N et al (2002) Screening E-cadherin in gastric cancer families reveals germline mutations only in hereditary diffuse gastric cancer kindred. Hum Mutat 5:510–517
8. Brooks-Wilson AR, Kaurah P, Suriano G et al (2004) Germline E-cadherin mutations in hereditary diffuse gastric cancer: assessment of 42 new families and review of genetic screening criteria. J Med Genet 7:508–517
9. Masciari S, Larsson N, Senz J et al (2007) Germline E-Cadherin mutations in familial lobular breast cancer. J Med Genet 44:726–731
10. Graziano F, Humar B, Guilford P (2003) The role of the E-cadherin gene (CDH1) in diffuse gastric cancer susceptibility: from the laboratory to clinical practice. Ann Oncol 12:1705–1713
11. Berx G, Becker KF, Hoffer H et al (1998) Mutations of the human E-cadherin (CDH1) gene. Hum Mutat 4:226–237
12. Aberle H, Schwartz H, Kemler R (1996) Cadherin-catenin complex: protein interactions and their implications for cadherin function. J Cell Biochem 4:514–523
13. Thoreson MA, Anastasiadis PZ, Daniel JM et al (2000) Selective uncoupling of p120(ctn) from E-cadherin disrupts strong adhesion. J Cell Biol 1:189–202
14. Xiao K, Oas RG, Chiasson CM et al (2007) Role of p120-catenin in cadherin trafficking. Biochim Biophys Acta 1:8–16

15. Vlemingck K, Vakaet L Jr, Mareel M et al (1991) Genetic manipulation of E-cadherin expression by epithelial tumor cells reveals an invasion suppressor role. Cell 1:107–119

16. Wijnhoven BP, Djinis WN, Pignatelli M (2000) E-cadherin-catenin cell–cell adhesion complex and human cancer. Br J Surg 8:992–1005

17. Novak A, Dedhar S (1999) Signaling through beta-catenin and LEF/Tcf. Cell Mol Life Sci 5:6:523–537

18. Orsulic S, Huber O, Aberle H et al (1999) E-cadherin binding prevents beta-catenin nuclear localization and beta-catenin/LEF-1-mediated transcription. J Cell Sci Pt 8:1237–1245

19. Aoki K, Taketo MM (2007) Adenomatous polyposis coli (APC): a multi-functional tumor suppressor gene. J Cell Sci Pt 19:3327–3335

20. Carneiro F, Huntsman DG, Smyrk TC et al (2004) Model of the early development of diffuse gastric cancer in E-cadherin mutation carriers and its implications for patient screening. J Pathol 2:681–687

21. De Leeuw WJ, Berx G, Vos CB et al (1997) Simultaneous loss of E-cadherin and catenins in invasive lobular breast cancer and lobular carcinoma in situ. J Pathol 4:404–411

22. Becker KF, Atkinson MJ, Reich U et al (1994) E-cadherin gene mutations provide clues to diffuse type gastric carcinomas. Cancer Res 14:3845–3852

23. Becker KF, Hoffer H (1995) Frequent somatic allelic inactivation of the E-cadherin gene in gastric carcinomas. J Natl Cancer Inst 14:1082–1084

24. Machado JC, Soares P, Carneiro F et al (1999) E-cadherin gene mutations provide a genetic basis for the phenotypic divergence of mixed gastric carcinomas. Lab Invest 79:459–465

25. Carneiro F, Oliveira C, Suriano G et al (2007) Molecular pathology of familial gastric cancer. J. Clin. Pathol

26. Grady WM, Willis J, Guilford PJ et al (2000) Methylation of the CDH1 promoter as the second genetic hit in hereditary diffuse gastric cancer. Nat Genet 1:16–17

27. Thull DL, Vogel VG (2004) Recognition and management of hereditary breast cancer syndromes. Oncologist 1:13–24

28. Rosman DS, Kaklamani V, Pasche B (2007) New insights into breast cancer genetics and impact on patient management. Curr Treat Options Oncol 1:61–73

29. CHEK2 Breast Cancer Case-Control Consortium (2004) CHEK2*1100delC and susceptibility to breast cancer: a collaborative analysis involving 10,860 breast cancer cases and 9,065 controls from 10 studies. Am J Hum Genet 6:1175–1182

30. Seal S, Thompson D, Renwick A et al (2006) Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance susceptibility genes. Nat Genet 5:518–525

31. Rahman N, Seal S, Thompson D et al (2007) PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat Genet 2:165–167

32. Ahmed M, Rahman N (2006) ATM and breast cancer susceptibility. Oncogene 43:5906–5911

33. Arpino G, Bardou VJ, Clark GM et al (2004) Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res 3:R149–156

34. Allen-Brady K, Camp NJ, Ward JH et al (2005) Lobular breast cancer: excess familiarity observed in the Utah Population Database. Int J Cancer 4:655–661

35. Lakhani SR, Gusterson BA, Jacquemier J et al (2000) The pathology of familial breast cancer: histological features of cancers in families not attributable to mutations in BRCA1 or BRCA2. Clin Cancer Res 3:782–789

36. Moll R, Mitze M, Frixen Uh et al (1993) Differential loss of E-cadherin expression in infiltrating ductal and lobular breast carcinomas. Am J Pathol 6:1731–1742

37. Berx G, Van Roy F (2001) The E-cadherin/catenin complex: an important gatekeeper in breast cancer tumorigenesis and malignant progression. Breast Cancer Res 5:289–293

38. Berx G, Clifton-Jansen AM, Strumane K et al (1996) E-cadherin is inactivated in a majority of invasive human lobular breast cancers by truncation mutations throughout its extracellular domain. Oncogene 9:1919–1925

39. Berx G, Clifton-Jansen AM, Nollet F et al (1995) E-cadherin is a tumour/invasion suppressor gene mutated in human lobular breast cancers. EMBO J 24:6107–6115

40. Droufakou S, Deshmene V, Roylance R et al (2001) Multiple ways of silencing E-cadherin gene expression in lobular carcinoma of the breast. Int J Cancer 3:404–408

41. Machado JC, Oliveira C, Carvalho R et al (2001) E-cadherin gene (CDH1) promoter methylation as the second hit in sporadic diffuse gastric carcinoma. Oncogene 12:1525–1528

42. Humar B, Toro T, Graziano F et al (2002) Novel germline CDH1 mutations in hereditary diffuse gastric cancer families. Hum Mutat 5:518–525

43. Sarrio D, Moreno-Bueno G, Hardisson D et al (2003) Epigenetic and genetic alterations of APC and CDH1 genes in lobular breast cancer: relationships with abnormal E-cadherin and catenin expression and microsatellite instability. Int J Cancer 2:208–215

44. Rahman N, Stone JG, Coleman G et al (2000) Lobular carcinoma in situ of the breast is not caused by constitutional mutations in the E-cadherin gene. Br J Cancer 3:568–570

45. Salahshor S, Huixin L, Huo H et al (2001) Low frequency of E-cadherin alterations in familial breast cancer. Breast Cancer Res 3:199–207

46. Lei H, Sjoberg-Margolin S, Salahshor S et al (2002) CDH1 mutations are present in both ductal and lobular breast cancer, but promoter allelic variants show no detectable breast cancer risk. Int J Cancer 2:199–204

47. Pharoah PD, Guilford P, Caldás C et al (2001) Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology 6:1348–1353

48. Fisher B, Costantino J, Redmond C et al (1989) A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N Engl J Med 8:479–484

49. Land SR, Wickerham DL, Costantino JP et al (2006) Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 23:2742–2751

50. Wolmark N, Dunn BK (2001) The role of tamoxifen in breast cancer prevention: issues sparked by the NSABP Breast Cancer Prevention Trial (P-1). Ann NY Acad Sci 99–108

51. Rebbeck TR, Friebel T, Lynch HT et al (2004) Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 6:1055–1062

52. Robson M, Svahn T, McCormick B et al (2005) Appropriateness of breast-conserving treatment of breast carcinoma in women with germline mutations in BRCA1 or BRCA2: a clinic-based series. Cancer 1:44–51

53. van Kouwen MC, Drenth JP, Oye WJ et al (2004) [18F]Fluoro-2-deoxy-D-glucose positron emission tomography detects gastric carcinoma in an early stage in an asymptomatic E-cadherin mutation carrier. Clin Cancer Res 19:6456–6459
54. Shaw D, Blair V, Framp A et al (2005) Chromoendoscopic surveillance in hereditary diffuse gastric cancer: an alternative to prophylactic gastrectomy? Gut 4:461–468
55. Huntsman DG, Carneiro F, Lewis FR et al (2001) Early gastric cancer in young, asymptomatic carriers of germ-line E-cadherin mutations. N Engl J Med 25:1904–1909
56. Norton JA, Ham CM, Van Dam J et al (2007) CDH1 truncating mutations in the E-cadherin gene: an indication for total gastrectomy to treat hereditary diffuse gastric cancer. Ann Surg 6:873–879
57. Lynch HT, Grady W, Suriano G et al (2005) Gastric cancer: new genetic developments. J Surg Oncol 3:114–133; discussion 133
58. Sjoblom T, Jones S, Wood LD et al (2006) The consensus coding sequences of human breast and colorectal cancers. Science 5797:268–274
59. Antoniou A, Pharoah PD, Narod S et al (2003) Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unsSELECTED for family history: a combined analysis of 22 studies. Am J Hum Genet 5:1117–1130
60. Jakubowska A, Nej K, Huzarski T et al (2002) BRCA2 gene mutations in families with aggregations of breast and stomach cancers. Br J Cancer 8:888–891
61. Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium (1999) J Natl Cancer Inst 15:1310–1316
62. Figer A, Irmlin L, Geva R et al (2001) The rate of the 6174delT founder Jewish mutation in BRCA2 in patients with non-colonic gastrointestinal tract tumours in Israel. Br J Cancer 4:478–481
63. Risch HA, McLaughlin JR, Cole DE et al (2001) Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet 3:700–710
64. Brose MS, Rebbeck TR, Calzone KA et al (2002) Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst 18:1365–1372
65. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, Cruz-Correa M, Offerhaus JA (2000) Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 6:1447–1453
66. Starink TM, van der Veen JP, Arwert F et al (1986) The Cowden syndrome: a clinical and genetic study in 21 patients. Clin Genet 3:222–233
67. Brownstein M.H., Wolf M., Bikowski J.B. (1978) Cowden's disease: a cutaneous marker of breast cancer. Cancer 6:2393–2398
68. Hambly LS, Lee EY, Schwartz RW (1995) Parathyroid adenoma and gastric carcinoma as manifestations of Cowden's disease. Surgery 1:115–117
69. Birch JM, Alston RD, McNally RJ et al (2001) Relative frequency and morphology of cancers in carriers of germ line TP53 mutations. Oncogene 34:4621–4628
70. Chompret A, Abel A, Stoppa-Lyonnet D et al (2001) Sensitivity and predictive value of criteria for p53 germ line mutation screening. J Med Genet 1:43–47
71. Keller G, Vogelsang H, Becker I et al (2004) 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 6:849
72. Kim IJ, Kang HC, Shin Y et al (2004) A TP53-truncating germline mutation (E287X) in a family with characteristics of both hereditary diffuse gastric cancer and Li-Fraumeni syndrome. J Hum Genet 49:591–595
73. Oliveira C, Ferreira P, Nabais S et al (2004) E-Cadherin (CDH1) and p53 rather than SMAD4 and Caspase-10 germline mutations contribute to genetic predisposition in Portuguese gastric cancer patients. Eur J Cancer 12:1897–1903
74. Kimura K, Shinmura K, Yoshimura K et al (2000) Absence of germline CHK2 mutations in familial gastric cancer. Jpn J Cancer Res 9:875–879
75. Shimoyama S, Aoki F, Kawaraha M et al (2004) Early gastric cancer development in a familial adenomatous polyposis patient. Dig Dis Sci 2:260–265
76. K. A. Schrader et al.
77. Very high risk of cancer in familial Peutz-Jeghers syndrome. Carcinogenesis 8:1655–1660