Family History and the Risk of Breast and Gastric Cancer

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Abstract

Epidemiologists have used family history, usually of first-degree relatives, as a marker for genetic risk, knowing that family history reflects the consequences of genetic susceptibilities, shared environment, and common behaviors. The role of family history on breast and gastric cancer risk has been evaluated in multiple studies. As for breast cancer, informative, valid, and precise estimates of the role of family history derive from a reanalysis of individual data from 52 epidemiologic studies including over 58,000 women with breast cancer and 100,000 controls, which estimated an approximately twofold increased risk for women with family history; the risk increased with the number of affected relatives, decreased with age and was greater the younger the relatives were when their breast cancer was diagnosed. As for gastric cancer, a meta-analysis published in 2018 and based on 36 case-control and 4 cohort studies found a significant pooled relative risk of about 2; in line with that, a subsequent analysis based on individual participant data from 17 studies participating in the Stomach cancer Pooling (StoP) Project found an 80% increased risk in subject with at least on first-degree relative affected by gastric cancer.

1.1 Familial Breast Cancer

Worldwide, breast cancer is the most common cancer in women, accounting for around 12% of all female cancers [1]. Most breast cancers are sporadic and not associated with high penetrance gene mutations. A woman's risk of developing

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breast cancer is increased if she has a family history of the disease. In fact, family history is a widely recognized risk factor for breast cancer. About 20% of breast cancer patients have a family history of the disease and in one-fourth of these cases breast cancer appears to be inherited in an autosomal dominant fashion [2].

Hereditary breast cancer is associated with germline mutations in the BRCA1 and BRCA2 genes and is characterized by early onset and bilateral disease. Rare mutations in these susceptibility genes confer a 10–30 times higher risk of developing the disease compared to the general population [3]. BRCA1 and BRCA2 are high penetrance genes involved in DNA repair and DNA damage response [4, 5]. BRCA1 was located on chromosome 17q using linkage analysis in site-specific breast cancer families [6]. BRCA2 is localized on chromosome 13 [7]. Breast cancer risk is increased in women carrying a germline mutation in either BRCA1 or BRCA2. These mutations are responsible for the Hereditary Breast/Ovaric Cancer (HBOC) Syndrome. BRCA1 and BRCA2 mutations are inherited in an autosomal dominant fashion but behave as recessive alleles in somatic cells [8].

Disruptive mutations in the BRCA1 gene include an 11-base pair deletion, a 1-base pair insertion, a stop codon, a missense substitution, and a regulatory mutation [9].

The association between family history of breast cancer and breast cancer risk has been investigated in numerous epidemiologic studies. A comprehensive systematic review and meta-analysis published in 1997 and including 52 case-control and 33 cohort studies gave a pooled estimate of familial relative risk (RR) of 1.9 (95% confidence interval, CI 1.7–2.0) for any affected relative and 2.1 (95% CI 2.0–2.2) for an affected first-degree relative. In analyses by type of relative affected, the pooled RR were 1.8 (95% CI 1.6–2.0) for daughter, 2.0 (95% CI 1.8–2.1) for mother, 2.3 (95% CI 2.1–2.4) for sister, and 3.6 (95% CI 2.5–5.0) for mother and sister. Risks were increased in subjects under age 50 and when the relative had been diagnosed before age 50 [10].

After that review, Negri et al. [11] conducted in Italy a hospital-based case-control study on 2569 women aged less than 75 years with histologically confirmed incident breast cancer and 2588 control women admitted to hospitals for non-neoplastic condition. Compared with women with no history of breast cancer in first-degree relatives, the odds ratio (OR) for family history was 2.4 (95% CI 1.9–3.0), corresponding to an overall population attributable fraction (PAF) of approximately 7%. Women with only the mother affected had an OR of 2.26 (95% CI 1.6–3.2), those with only sister(s) an OR of 2.56 (95% CI 1.9–3.5), and those with both the mother and sister(s) affected an OR of 2.36 (95% CI 0.8–7.0). The PAF at all ages was 2.86% for mothers' history (95% CI 1.78–3.93), 3.15% for sisters' (95% CI 2.10–4.19), and 1.11 for other/combined (95% CI 0.46–1.76) [12].

In a population-based study of the Swedish Family-Cancer Database on 10.2 million individuals and more than 5500 familial breast cancers, Hemminki et al. [13] estimated familial standardized incidence ratios (SIR) of breast cancer of 1.79 by breast cancer in the mother only, 2.03 by breast cancer in a sister only, and 2.82 by breast cancer in both a mother and sister, and a PAF for familial breast cancer of 7.05% (3.61% for mother history, 3.01% for sister, 0.43% for both). The PAF values

Table 1.1 Risk ratios for breast cancer by number of first-degree relatives with a history of breast cancer, and for having a relative diagnosed with breast cancer at <40 years in strata of woman's age[a] from the Collaborative Group on Hormonal Factors in Breast Cancer analysis [14]

	Cases ($n = 58,209$)	Controls ($n = 101,986$)	Risk ratio (99%CI)[a]	Risk ratio for women <50 years (99%CI)	Risk ratio for women ≥50 years (99% CI)
Number of first-degree relatives with breast cancer					
None	50,713	94,548	1.0 (0.97–1.03)	Ref.	Ref.
1	6810	6998	1.80 (1.70–1.91)	2.14 (1.92–2.38)	1.65 (1.53–1.78)
2	603	404	2.93 (2.37–3.63)	3.84 (2.37–6.22)	2.61 (2.03–3.34)
3 or more	83	36	3.90 (2.03–7.49)	12.5 (1.70–85.16)	2.65 (1.29–5.46)
Relative's age at diagnosis of breast cancer <40 years[b]					
Woman's age (years)					
<40	125	41	5.7 (2.7–11.8)		
40–49	132	76	3.0 (1.8–4.9)		
50–59	94	107	2.0 (1.2–3.4)		
≥60	87	122	1.4 (0.9–2.1)		

CI: confidence interval

[a] Risk ratios are calculated as floating absolute risk (FAR, with FAR = 1.0 for women with no affected relative)

[b] The ref. category of the risk ratio is the group of women in the same age category with no affected relative

decreased by age when the daughter had a mother history of breast cancer but not when she had a sister history, and were not associated with the morphologic type of breast cancer.

In 2001, a re-analysis of individual data from 52 epidemiologic studies on familial breast cancer including 58,209 women with breast cancer and 101,986 control women confirmed the increased risk of breast cancer among women with a family history of the disease [14] (Table 1.1). Risk ratios for breast cancer were 1.80 (95% CI 1.69–1.91), 2.93 (95% CI 2.36–3.64), and 3.90 (95% CI 2.03–7.49) for one, two, and three or more affected first-degree relatives, respectively. The excess risk decreased with age and was greater the younger the relatives were when their breast cancer was diagnosed. Similar increased risks were observed according to the type of affected relative. In any case, most women who developed breast cancer did not have an affected first-degree relative. Authors estimated cumulative incidence of breast cancer up to age 50 of 1.7%, 3.7%, and 8.0% for women with zero, one, or two affected first-degree relatives, respectively, in more-developed countries; corresponding estimates for incidence up to age 80 were 7.8%, 13.3%, and 21.1%, and for death from breast cancer up to age 80 were 2.3%, 4.2%, and 7.6%.

More recently, Kuchenbaecker et al. [15] estimated cumulative risks of breast cancer for BRCA1 and BRCA2 mutation carriers using data from a prospective cohort. The cumulative risk of developing breast cancer by age 80 years was 72% for BRCA1 mutation carriers and 69% for BRCA2 mutation carriers, respectively. The cumulative risk to age 50 years were higher for BRCA1 carriers. In addition, breast cancer risk was higher if BRCA1 mutations were located outside vs within the regions bounded by positions c.2282 to c.4071 (hazard ratio, HR = 1.46; 95% CI 1.11–1.93).

Research has made significant further efforts to identify other susceptibility genes for breast cancer that also operate in the DNA damage response. TP53 is a tumor suppressor gene that causes Li Fraumeni syndrome [16]. TP53 mutation carriers are predisposed to a variety of different tumors, including sarcomas, brain tumors, breast cancers, and adrenocortical carcinomas, diagnosed before the age of 45 years [17]. In 265 families with a germline TP53 mutation or affected with Li-Fraumeni syndrome, breast cancer was the most frequent malignancy (30.6%), followed by soft tissue sarcoma (17.8%), brain tumor (14%), and adrenocortical carcinoma (6.5%). All of the breast cancers were in female TP53 mutation carriers [18].

The ATM gene encodes a protein kinase with an important role in DNA repair [19]. Biallelic mutations in the ATM gene cause ataxia-telangiectasia, a rare autosomal recessive neurological disorder characterized by cancer predisposition, in particular lymphomas and leukemia [20]. By contrast, heterozygous female ATM mutation carriers are at elevated risk of breast cancer [21]. Thompson et al. [22] observed a significant excess of female breast cancer in heterozygous female ATM mutation carriers (RR = 2.23, 95% CI 1.16–4.28) compared with the general population, but the RR was 4.94 (95%IC, 1.90–12.9) in women younger than age 50 years. A meta-analysis published in 2016 estimated a pooled RR of 3.0 (95% CI 2.1–4.5) of breast cancer in female obligate ATM heterozygotes [23].

Another gene that confers susceptibility to breast cancer is the CHEK2 gene, which encodes a kinase protein involved in DNA repair [24]. The CHEK2*1100*del*C mutation confers an about twofold increased breast cancer risk in women and a tenfold increased risk in men. This truncating mutation was found in 5.1% of individuals with breast cancer from families without BRCA1 or BRCA2 mutation [25]. By contrast, its frequency is of 1.1% in the healthy population. In a large case-control study conducted in Poland a truncating CHECK mutation (1100delC) was present in 227 (3%) of 7496 women with breast cancer and in 37 (0.8%) of 4346 controls (OR = 3.6, 95% CI 2.6-5.1). The OR was higher for women with a first- or second-degree relative with breast cancer (OR = 5.0, 95% IC 3.3–7.6) than for women with no family history (OR = 3.3; 95% CI 2.3–4.7) [26]. The authors estimated the lifetime risk of breast cancer for CHEK2*1100delC carriers to be 20% for women with no affected relative. Female homozygotes for the CHEK2*1100delC have a risk of breast cancer increased more than twice the risk of heterozygous carriers [27].

In conclusion, epidemiological evidence indicates an approximately twofold increased breast cancer risk associated with family history of the disease. In any case, most women who develop breast cancer do not have an affected relative. Still,

in high-income countries women with a first-degree relative with breast cancer have an over 10% lifetime cumulative risk of developing breast cancer [14].

1.2 Familial Gastric Cancer

Gastric cancer is a global health problem, with more than one million incident cases worldwide each year, ranking fifth for incidence and fourth for mortality globally in 2020 [1]. The classification of Lauren distinguishes two main types of gastric carcinoma, diffuse gastric cancer and intestinal-type gastric cancer, which display different molecular, epidemiologic, and morphologic features [28].

Although gastric cancer is usually sporadic, it occurs more frequently among close relatives of affected patients than in the general population. Familial aggregation is observed in about 10% of cases [29, 30]. The importance of family history, a proxy of hereditary and genetic factors, as a risk factor for gastric cancer has been evaluated in several studies, mostly case-control studies [31]. In general, these studies gave estimates of the familial RR of gastric cancer ranging from 1.5 to 3, with however a few studies from Asia, where the rate of the disease is notoriously higher compared with Western countries, providing dramatically elevated RR, over 6–7. Differences in the strength of the association across studies conducted in various populations may be in part attributed to their different baseline characteristics, lifestyle habits, and rates of gastric cancer.

Among the earliest studies, a hospital-based case-control study in Italy studied the familial occurrence of cancer in 154 patients with gastric cancer registered in 1986 and 1987 and in 154 controls matched by age and sex by tracing a careful genealogical tree of first-degree relatives [29]. Thirty first-degree relatives with gastric cancer were reported in case families (3.3%) versus 15 in control families (1.5%), for a corresponding OR of 3.14 ($p < 0.01$). The excess of gastric cancer was more marked in siblings (OR = 4.33, $p < 0.02$) than in parents (OR = 1.61, not significant). No significant excess of other types of cancers in case families was observed. In another Italian hospital-based case-control study conducted in 1985–1991 and including 628 cases and 1776 controls, the prevalence of family history of gastric cancer was 12.6% among cases and 4.9% among controls. The corresponding OR adjusted for age, sex, area of residence, education, and number of siblings was 2.6 (95% CI 1.8–3.6), being similar for having affected parents (OR = 2.4, 95% CI 1.7–3.4) and affected siblings (OR = 2.5, 95% CI 1.3–4.6), and directly related with the number of first-degree relatives affected. In terms of PAF, approximately 8% of gastric cancers in that population were related to the familial component [30].

Several case-control studies were published thereafter. Among the larger ones, a study from Poland [32] showed an over threefold increase in risk for a history of gastric cancer in first-degree relative (OR = 3.5, 95% CI 2.0–6.2) based on 464 cases and 480 controls. The OR for family history was 6.6 for affected parents (95% CI 4.20–10.40) and 10.1 for affected siblings (95% CI 6.10–16.82) in a hospital-based case-control study carried out in Turkey with 1240 cases and 1240 controls [33, 34], and 3.67 (95% CI 2.01–6.71) in a case-control study from Spain with 404 cases and

404 controls [35]. In a large population-based case-control study conducted in Japan (1400 cases, 13,467 controls) the OR for family history was greater in the younger age group (≤43 years) than in the older age group (>43 years), i.e., 6.3 (95% CI 4.1–9.9) and 4.4 (95% CI 3.9–5.0), respectively [36].

Only a few prospective cohort studies, mainly from Asia, evaluated family history as a risk factor for gastric cancer, with mixed results. In a large cohort study, in which 19,028 individuals from the Japanese Public Health Center cohort II were followed-up from 1993 to 2009, gastric cancer history in first-degree relatives was associated with an increased risk gastric cancer with a HR of 1.30 (95% CI 1.25–1.35), based on 412 incident cases [37]. In a Japanese case-control study nested in a cohort, family history of gastric cancer in first-degree relatives was associated with an increased risk of the disease in women, but not in men, after controlling for *Helicobacter pylori* infection and other confounding variables, with RR of 1.73 (95% CI 0.82–3.65) and 0.89 (95% CI 0.40–1.97), respectively [38]. Only one cohort study was conducted in a Western population, specifically in Finland. A total of 307 incident gastric cancer cases among 20,720 male smokers were identified during the follow-up period. Gastric cancer history in any first-degree relatives was associated with an approximately 1.5-fold increased gastric cancer, after adjustment for age, number of siblings, body mass index, smoking, alcohol, education, and fruit and vegetable intake (HR = 1.56, 95% CI 1.15–2.12) [39].

In 2018, a meta-analysis including 40 observational studies was published. The pooled RR for family history of gastric cancer was 2.31 (95% CI 1.99–2.68) from all studies ($n = 40$), 2.56 (95% CI 2.12–3.10) from case-control studies ($n = 36$), and 1.30 (95% CI 1.26–1.34) from cohorts ($n = 4$). Family history of gastric cancer was significantly associated with non-cardia (pooled RR = 1.97, 95% CI 1.72–2.25), but not with cardia gastric cancer (pooled RR = 1.46, 95% CI 0.89–2.39). The association appeared stronger for family history of gastric cancer in siblings (pooled RR = 2.84, 95% CI 1.91–4.24) than in parents (pooled RR = 2.16, 95% CI 1.68–2.76) [39].

More recently, the association between family history of gastric cancer and gastric cancer risk was investigated within a large consortium of epidemiological studies on gastric cancer, the Stomach cancer Pooling (StoP) Project [40]. The analysis was based on 5949 cases of gastric cancer and 12,776 controls from 17 case-control studies from 11 countries. Most studies were conducted in Europe (82.3% of the controls and 77.9% of the cases). Family history of gastric cancer resulted directly related with gastric cancer with a pooled OR of 1.8 (95% CI 1.64–2.04), in the absence of material heterogeneity among studies ($I^2 = 6.1\%$, $P_{\text{heterogeneity}} = 0.838$) (Fig. 1.1). The pooled OR was higher for having affected siblings than affected parents (OR =1.6, 95% CI 1.20–2.05, and OR = 1.5,95% CI 1.28–1.80, respectively). There were no significant differences among subgroups by sex, age, geographic area, or study period. In that pooled investigation, family history has a greater pooled OR on non-cardia (OR = 1.82, 95% CI 1.59–2.05) than cardia gastric cancer (OR = 1.38, 95% CI 0.98–1.77). The occurrence of non-cardia gastric cancer is mainly attributed to

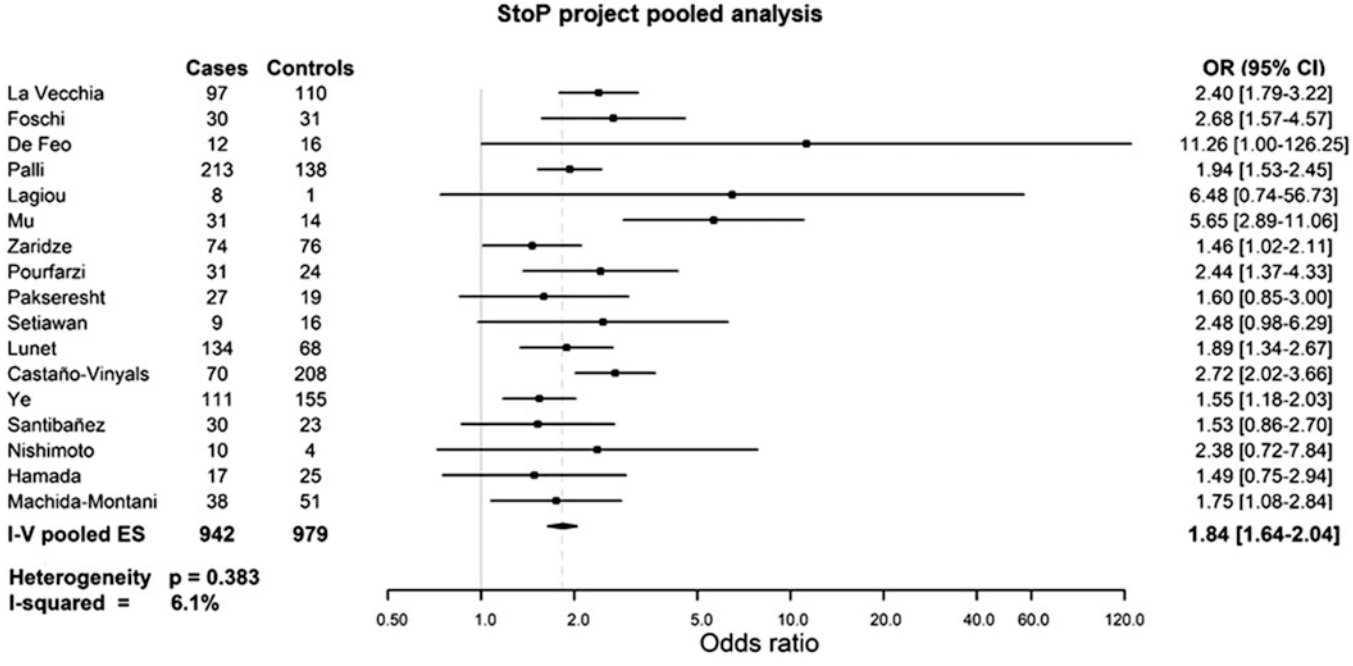

Fig. 1.1 Study-specific and pooled adjusted odds ratios (OR) with corresponding 95% confidence intervals (CI) of gastric cancer for family history of gastric cancer in first-degree relatives in the StoP Project [40]

Helicobacter pylori atrophic gastritis and, therefore, is more likely associated with familial clustering [41]. On the other hand, cardia gastric cancer is more likely related to lifestyle factors, such as obesity, gastroesophageal reflux, western diet, and tobacco smoking [40–45].

The familial aggregation of gastric cancer is due to a complex interaction between genetic inheritance and environmental and lifestyle factors. It is known that between 10% and 20% of people who develop gastric cancer have family history, but only part of this can be attributed to a hereditary syndrome. The estimates based on family history involve both genetic and shared environment factors, specifically *H. pylori*, which is the primary risk factor in gastric carcinogenesis and tends to cluster in families [46]. However, in the pooled analysis within the Stop Project the association with family history of gastric cancer was similar in subgroups defined by *H. pylori* infection [40].

A combination of linkage and mutation analysis identified in an extended New Zealand Maori family with early onset diffuse gastric cancer the gene for the cell-to-cell adhesion protein *E-cadherin* as a cancer-susceptibility gene [47]. Epithelial cadherin is a cell adhesion protein predominantly expressed in epithelial tissue. This cell adhesion molecule plays an important role in establishing cell polarity and maintaining epithelial tissue morphology. *E-cadherin* molecules are generally localized at the basolateral surface of the cell, in a region of cell-cell contact that is known as zonula adherences junctions [48, 49]. E-cadherin is encoded by CDH1 that maps to chromosome 16q22.1. Sequencing of the *E-cadherin* gene revealed a G T nucleotide substitution (position 1008) of 7 exon, leading to a truncated gene product. To confirm the role of *E-cadherin* in hereditary gastric cancer susceptibility, the authors identified *E-cadherin* germline truncating mutations in two other families of Maori ethnicity with early-onset diffuse gastric cancer. This first genetic linkage study demonstrated the role of *E-cadherin* germline mutations in familial diffuse gastric cancer [47]. Shortly afterward, *E-cadherin* germline truncating mutations were detected in three families of European origin with familial diffuse gastric cancer [50] and subsequently, *E-cadherin* germline mutations have been identified in similar families from several countries reinforcing the role of *CDH1* in susceptibility to diffuse gastric cancer in other populations. The first *CDH1* germline missense mutation has been described in an Italian family with hereditary diffuse gastric cancer [51]. All of these families have diffuse-type gastric cancer and *CDH1* germline mutations have not been described in eight families of European origin with intestinal gastric cancer [50]. This specificity of tumor type has led to the identification of this new familial cancer syndrome, designated Hereditary Diffuse Gastric Cancer (HDGC), characterized by high prevalence of diffuse gastric cancer and lobular breast cancer [52, 53]. Heterozygous carriers of a *E-cadherin* germline mutation have a high lifetime risk of developing gastric cancer and lobular breast cancer. The cumulative risk of gastric cancer in *CDH1* mutation carriers increases steadily from early adulthood. The estimated cumulative risk of diffuse gastric cancer in mutation carriers by age 80 years was 67% for men (95% CI 39–99%) and 83% for women (95% CI, 58–99) [54]. In 1999, specific clinical criteria have been set to select individuals for *CDH1* genetic screening. Using the first guidelines

established in 1999 the detection rate of *CDH1* mutations was approximately 40% in individuals fulfilling the clinical criteria [55]. However, the guidelines were subsequently revised given that *CDH1* germline mutations were also identified in individuals who did not meet testing criteria. Hansford and colleagues [56] reported in the largest series of *CDH1* mutations carriers that the cumulative risk of diffuse gastric cancer by age 80 years was 70% (95% CI 59–80%) for men and 56% (95% CI 44–69%) for women, whereas breast cancer lifetime risk for women was 42% (95% CI 23–68%). HDGC caused by germline *CDH1* mutations is an autosomal dominant cancer syndrome.

Different patterns of *CDH1* germline mutations have been described as missense, non-sense, deletion, and splice-site. Insertions are less frequently described, constituting about 10% of all *CDH1* mutations. Corso and colleagues [57] verified that the predominant mutation type varies across geographical regions. Deletions are more frequent in Europe (34%), splice-site in America (48%), missense in Asia (68%), and non-sense in Oceania (78%). There are few other genes which are involved in HDGC predisposition, including *CTNNA1*. Like *CDH1*, *CTNNA1* is involved in intercellular adhesion. Germline *CTNNA1* alterations cause HDGC on occasion and should be considered in screening of prospective families [53].

It is therefore important to take into account the presence of a gastric cancer history in first-degree relatives to carry out gastric cancer early diagnosis.

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