Journal 0f Medicine and Medical Sciences Vol. 1(8) pp. 372-384 September 2010
Available online http://www.interesjournals.org/JMMS

Full Length Research Paper

A theory that explains the tissue specificity of BRCA1/2 related and other hereditary cancers

Bernard Friedenson

Department of Biochemistry and Molecular Genetics College of Medicine, University Illinois Chicago, Chicago, IL 60607. Email: molmeddoc@gmail.com

Accepted 14 September, 2010

Women who inherit a defective BRCA1 or BRCA2 gene have risks for breast and ovarian cancer that are so high and seem so selective that many mutation carriers choose to have prophylactic surgery. There has been much conjecture to explain such apparently striking tissue specificity. All these suggestions share the assumption that some disabled function of normal tumor suppressor genes leads to a tissue specific cancer response. Here the idea is proposed and tested that major determinants of where BRCA1/2 hereditary cancers occur are the tissue specificity of the cancer pathogen, the agent that causes chronic inflammation or the carcinogen. The target tissue may have receptors for the pathogen, become selectively exposed to an inflammatory process or to a carcinogen such as during digestion. An innate genomic deficit in a tumor suppressor gene such as BRCA1/2 contributes because it exacerbates the susceptibility to disease wherever it attacks. This hypothesis also fits data for several tumor suppressors beyond BRCA1/2. A major advantage of this model is that it suggests there may be some options in addition to prophylactic surgery.

Keywords: Hereditary cancer, inflammation, DNA repair, BRCA1, BRCA2, Fanconi.

INTRODUCTION

Women who inherit a defective BRCA1 or BRCA2 gene have risks for breast / ovarian cancer that are so high and apparently so selective that many mutation carriers choose to have the targets for cancer surgically removed (Rebbeck et al., 2009; King et al., 2003). This raises the question why cancer just attacks breasts and ovaries when every cell with a nucleus inherits the same mutation. Functionally, both BRCA genes are general cell requirements because they encode products essential for fundamental activities such as DNA repair. Why does inheriting a defect in general cell requirements lead to cancers in specific target organs? Answering these questions might help delay or prevent the onset of hereditary cancers.

One plausible explanation involves the high proliferative activity in ovary and breast tissues, especially when under the influence of estrogens. (Welcsh and King, 2001). Cells with an inherited deficit in BRCA1 or BRCA2 acquire a second mutation spontaneously in these tissues. Mutations in BRCA1 and BRCA2 genes may be more likely because of high frequencies of repetitive elements (Welcsh and King, 2001). Cells with mutations in both alleles then become repair deficient and acquire additional mutations even more readily. Tumors of BRCA1/2 carriers have more losses and gains than non-hereditary cancers (Jonsson et al., 2005; Joose et al., 2009). Most seriously abnormal cells die, but in rapidly proliferating breast epithelium some abnormal cells escape by acquiring critical checkpoint mutations. These cells may give rise to

Abbreviations

A-T-ataxia-telangiectasia
ATM-gene mutated in ataxia-telangiectasia
CI-confidence interval
DSB, DNA- double strand break
EBV- Epstein-Barr virus
FA-Fanconi anemia
HBV-hepatitis B virus
HNSCC-head and neck squamous cell carcinoma
HPV-human papilloma virus
DCIS-ductal carcinoma in situ
HR-hazard ratio
I^2-inconsistency statistic
MMTV-mouse mammary tumor virus
NK cells-natural killer cells
NSAIDs-non-steroidal anti-inflammatory drugs
OC-oral contraceptives
OR-odds ratio
RR-relative risk

cancers. One objection to this explanation is that other tissues and cells also have high proliferation rates but are not generally regarded as specific sites for tumor formation in BRCA1/2 mutation carriers. However, implicating BRCA1/2 and associated genes in lymphomas and leukemias does suggest that prolonged high proliferation rates contribute (Friedenson, 2007).

The predilection of BRCA1 carriers to develop cancers in breast and ovary suggests tissue specific activities that may be due in part to tissue specific transcription functions. While it has not been demonstrated that BRCA1 can interact directly with a sequence within undamaged DNA, BRCA1 can bind to various sequence-specific DNA binding transcription factors to alter transcription (Rosen et al., (2006). It is possible that BRCA1 may regulate certain genes expressed only in the breast and ovaries. The altered expression of these transcripts would lead to an increase in neoplastic transformation (Welcsh and King, 2001). However, risks for other cancers in organs beyond breast and ovary are increased as well, especially in children born with biallelic mutations in BRCA2 (Alter et al., 2007)

A major biochemical consequence of BRCA1 deficiency is the loss of functional complexes between BRCA1- and BRCA1-interacting proteins. BRCA1 contains several functional regions that interact with proteins including ATM, p53, RB, c-Myc, BRCA2, DNA repair factors, E2F, and others. Many of these are proto-oncogenes or tumor suppressors that can regulate transcription through both direct and indirect mechanisms. Thus BRCA1 is probably involved in multiple biologic programs of cellular behavior, including transcription, cell-cycle regulation, DNA damage repair, centrosome duplication, and cell growth and apoptosis. However, none of these BRCA1 interacting proteins show a tissue restricted pattern of expression that could explain the specific tissue tropism of BRCA1-related cancers (Gardner and Liu, 2001).

According to another conjecture, ovary- and breast-specific BRCA1 cofactors could cause transformation in the absence of BRCA1. The presence of hormonal survival factors may have a protective effect, allowing cells with inactive BRCA1/2 to survive and proliferate. Both the breast and ovaries are targets of estrogen and other hormones that endow anti-apoptotic survival functions. (Gompel et al. 2000). BRCA1 may play an inhibitory role in estrogen receptor (ER) signaling that could help explain the tissue specificity (Fan et al., 2001; Dizin and Imminger-Finger, 2010). However, most BRCA1 associated tumors lack ER expression and it is still unclear if such tumors arise from cells that never expressed ER or that subsequently lost ER expression. Tamoxifen use beginning at age 35 years or older did not reduce breast cancer incidence among healthy women with inherited BRCA1 mutations. Tamoxifen reduced ER positive breast cancer incidence among healthy BRCA2 carriers by about the same amount as in normal women (King et al., 2001).

This does not rule out some hormonal effects. In a prostate cancer model, hormone receptor complexes move regions of chromosomes into close proximity and increase risks for site specific cancer related gene fusions after DNA double strand breaks are induced by DNA radiation damage (Lin et al., 2009).

BRCA1 and BRCA2 gene products interact with recombination / DNA repair proteins in pathways that participate in preserving intact chromosome structure. It is unclear to what extent such functions specifically suppress breast and ovarian cancer (Scully and Livingston 2000). It is possible that impaired DNA repair processes themselves trigger cancer by allowing mutations to accumulate. This does not account for why cancer occurs in some tissues but not others.

Zhou and Elledge suggested that most tissues have alternative ways of performing BRCA1 or BRCA2 tumor suppressing functions but breast and ovary do not. Therefore, loss of normal BRCA1/2 proteins in tissues with alternate mechanisms has less effect. BRCA2 again challenges this conjecture because people survive with bi-allelic mutations in BRCA2. Thus every cell is capable of surviving with inactivated BRCA2. Zhou and Elledge (2002) proposed that BRCA1 and BRCA2 (like other tumor suppressors) acquire specificity by exploiting unique properties of their target tissues.

The above conjectures share the assumption that some innate function of the normal tumor suppressor genes leads to a tissue specific cancer response. In contrast a different hypothesis is proposed here that can be tested and fits the data. The tissue in which disease occurs is greatly influenced by the tissue specificity of the disease pathogen, of a specific chronic inflammatory process or of a carcinogen. The target tissue can contribute because it has receptors for the pathogen and provides an environment that allows disease. An innate genomic deficit contributes because it exacerbates the susceptibility to disease wherever it attacks.

This pathogen, inflammation, or carcinogen model of tissue specificity can be tested against a variety of independent and different lines of evidence. Some chronic infections can effectively direct cancer to a specific organ. For example, hepatitis viruses target the liver for cancer because the liver has receptors for hepatitis viruses (Machida et al., 2006; De Marzo et al., 2007). Many normal individuals recover and never develop liver cancer. Similarly, H. pylori infection induces genetic instability in the nuclei and mitochondria of gastric cells (Machado et al., 2009).

These inflammatory conditions mediated by known infections are related here to components within pathways mediated by BRCA1/2. Acetaldehyde, a

known carcinogen is causally linked to digestive tract and breast cancers, also has relationships to pathways containing BRCA1/2 and Fanconi anemia (FA) proteins. Many independent lines of evidence support the idea that damage mediated by tissue specific pathogens, chronic inflammation, or a carcinogen gives tissue specificity to BRCA1/2 related cancers. This model also accommodates data for other tumor suppressors.

MATERIALS AND METHODS

Test models for cancers with known relationships to pathogens or carcinogens

Cancers were chosen as initial test models because they all have widely accepted and well-known links to pathogens or the carcinogen acetaldehyde. Group 1: liver cancer associated with viral hepatitis such as hepatitis B or C or liver and digestive tract cancer associated with the carcinogen acetaldehyde from alcohol metabolism; Groups 2-4: vulvar, cervical, and head and neck cancers, all associated with human papilloma viruses (HPVs); and Group 5: stomach (gastric) cancer associated with helicobacter pylori. The literature was reviewed for associations between these agents and components within models for pathways containing BRCA1 and BRCA2.

Information sources

PubMed and Google Scholar databases were systematically searched up through 2010, initially for original studies of non-breast, non-ovarian cancers vs. any defect in a model for BRCA1/2 function (Figure 1). 1300 articles published in the past 50 years were retrieved and copied to a database to facilitate computer searching and review. Many bibliographies were also reviewed for additional relevant references that may have been missed. Explicit procedures were used to systematically identify, appraise, summarize and statistically aggregate relevant studies (Moher et al., 1999).

Statistical analyses

For meta-analyses, the random effects model was used (Dersimonian and Laird, 1986). P values were derived from two-sided statistical tests.

RESULTS AND DISCUSSION

Evidence for interactions between infections or a carcinogen linked to cancers and FA, BRCA1/2, and ATM

A composite model (Figure. 1) was derived incorporating numerous mechanistic studies that all picture BRCA1/2 functioning in a DNA repair pathway scheme together with FA proteins and ATM (D'andrea and Grompe, 2002; Venkitaraman, 2003; Bolderson et al., 2010; Pace et al., 2010; Cohn and D'Andrea, 2008; Whitby, 2010).

This derived pathway gives a general outline for repair of DNA interstrand cross-links, stalled replication forks and double strand breaks. Inherited defects in this repair outline were tested against risks for cancers with known links to pathogens, chronic inflammation and to acetaldehyde. Cancers of the liver, cervix, vulva, head-neck, and stomach were used as initial test tissue-specific cancers. Acetaldehyde from alcohol metabolism was used as a test for exposure to a carcinogen that causes DNA cross-links.

Multiple independent lines of evidence support the concept that pathogens, chronic inflammation or the carcinogen acetaldehyde greatly contribute to the tissue specificity of cancer in carriers of BRCA1, BRCA2, ATM and FA mutations. These different types of evidence are discussed below. In most cases each line of evidence is supported by multiple published observations.

Ten lines of evidence supporting pathogens or a carcinogen determining tissue specificity of hereditary BRCA1/2 or other hereditary cancers

Chronic inflammation in cancer models and increased susceptibility in mutation carriers

As a sign of chronic inflammation, lymphocyte infiltration is present in five organ specific model cancers caused by specific infections (liver, cervix, vulva, head-neck, and stomach cancers). Homozygous mutations in ATM or a FA gene cause the hereditary diseases ataxia-telangiectasia (A-T) or Fanconi anemia (FA) respectively. Both different homozygotes inherit a deficit in Fig. 1. A-T and FA patients have strong risk factors for viral hepatitis (and liver cancer) because they require multiple transfusions. Increased HCV seropositivity in Ashkenazi Jews (a group with high incidence of BRCA1/2 mutations) suggests that ethnic factors predispose to HCV transmission and infectivity (Golan et al., (1996). There is greater susceptibility to viral transformation in FA-C deficiency (Liu et al., 1996).

Responses to inflammation are abnormal in both A-T and FA (Ward et al., 1994; Ward and Rosin, 1993; Zanier et al., 2004; Rosselli et al.,1994; Suhasini et al., 2009; Saito et al., 2003; Sejas et al., 2007; Hadjur et al., 2001).

Mechanisms of DNA damage due to infections / inflammation suggest repair is required but infections may inhibit repairs

Infection and inflammation of many tissues is accompanied by upregulation of an inducible isoform of nitric oxide synthase that can produce excess nitric oxide for a prolonged period. Nitric oxide derived reactive

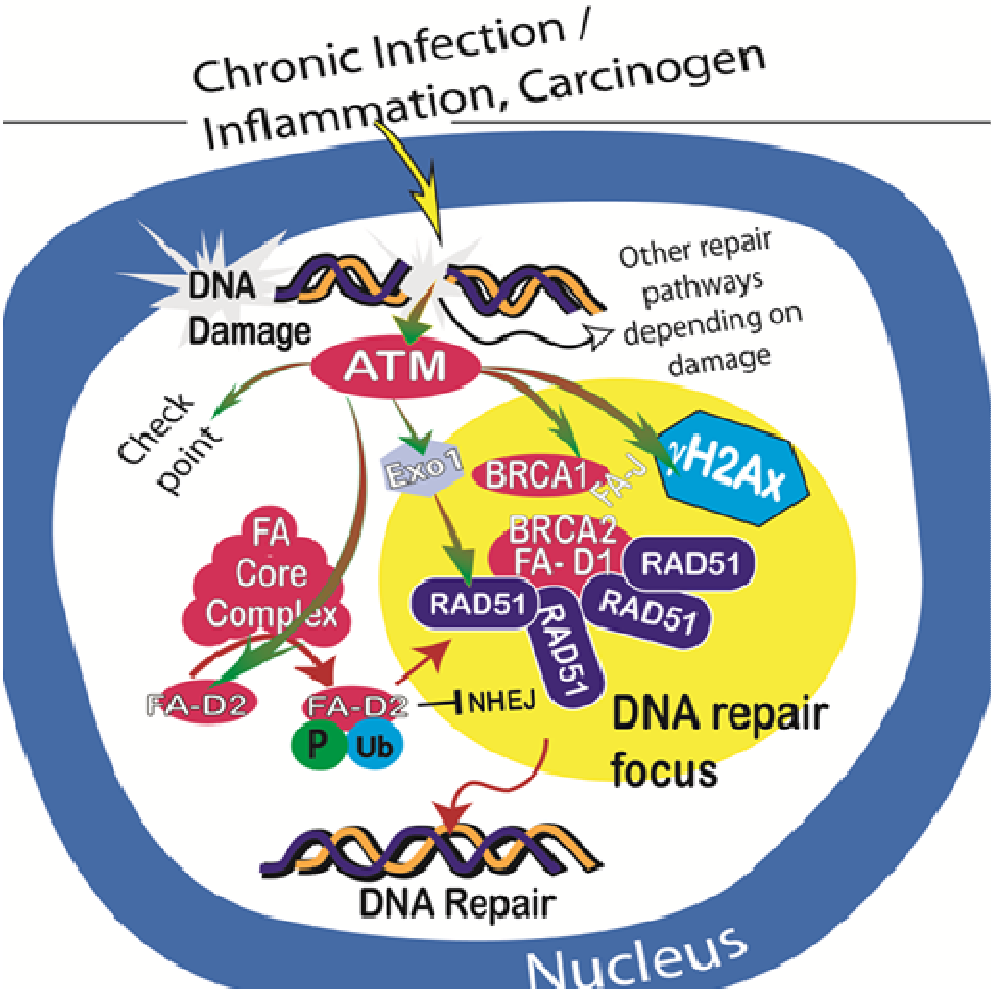

Figure 1. Working test model for Derived DNA repair pathway containing BRCA1 and BRCA2 gene products.

The model was compiled based on literature (D'Andrea and Grompe, 2002; Venkitaraman, 2003; Bolderson et al., 2010; Pace et al., 2010; Cohn and D'Andrea, 2008). For BRCA pathway components (colored red), risks have been studied in mutation carriers for multiple cancers linked to known infections and inflammation. The red components are involved in repairing complex damage that occurs during inflammation or from a carcinogen such as acetaldehyde. ATM is placed as initial signal transducer following detection of a double strand break. Human exonuclease 1 (Exo 1) is required for double strand break repair by homologous recombination. ATM is probably essential for rapid phosphorylation of Exo1. In turn Exo1 phosphorylation is essential to recruit Rad51. Phosphorylation of Exo1 by ATM is dispensable for resecting double strand breaks but this likely interferes with homologous recombination due to defective loading of Rad51 (Bolderson et al., (2010). ATM also induces a cell cycle checkpoint and phosphorylates BRCA1 and FA-D2. FA core complex proteins cause the ubiquitylation of FANCD2 which is then found in repair foci along with BRCA1 and BRCA2. FA-D2 might antagonize Ku70 activity and divert double-strand break repair away from abortive NHEJ and toward homologous recombination. Pace et al (2010). One member of the FA core complex, FA-M is a DNA junction-specific helicase / translocase that targets and processes perturbed replication forks and intermediates of homologous recombination (Whitby, 2010; Gari et al., 2008). Acetaldehyde from alcohol metabolism and inflammation also induce interstrand cross-links which characteristically require pathway components for repair. BRCA1 is essential to form nuclear foci, believed to be sites of DNA repair. BRCA2 aids the recruitment and loading of the RAD51 repair protein onto processed double strand breaks. ATR, a kinase closely related to ATM is activated later when stalled replication forks form during replication of damaged DNA (Bolderson et al. 2010). The ATR signaling cascade re-enforces ATM-induced cell cycle checkpoints. Cancer risks for FA were measured before all the components were known and refer to FA genes as a group. Not shown are numerous interactions involving BRCA1 or BRCA2 with other proteins, details of relationships to cell cycle checkpoints, and to estrogen signaling. The drawing represents a working model that may actually represent the sum of simultaneous pathways activated in response to complex inflammation or acetaldehyde related DNA damage, requiring several different types of repair. Inflammation also causes damage requiring other pathways for repair such as mismatch repair, base excision repair, etc.

species cause DNA damage and have carcinogenic potential (Sawa and Ohshima, 2006).
Although other factors also contribute to cancer, three pathogens strongly associated with cancer are well-known to cause double strand breaks by inflammatory processes. Specifically, HCV infection triggers mitochondrial changes releasing reactive oxygen and nitrogen species. This causes DNA double strand breaks (Machida et al., 2006). Similarly HPV-16 infection reduces reactive oxygen scavenging activity and makes cells unresponsive to H_2O_2 damage (Lembo et al., 2006). Infection with the bacteria h. pylori inhibits the ability to remove reactive oxygen intermediates by inhibiting scavenging enzymes (Smoot et al., 2000).

Association of gene defects in the Fig. 1 pathway with known infection / inflammation related cancers

54% of FA patients who develop cancers caused by HPV (e.g. cervical or head-neck cancer) have evidence of HPV infection as condyloma. In comparison to non-FA cancer patients, odds of finding HPV infection in HNSCC in FA patients are 8.85 [1.90 - 54.2] (Kutler et al., (2003a).

BRCA2 mutation increases risks for stomach cancer usually associated with h. pylori. The standardized incidence ratio for stomach cancer in 29 BRCA2 families was nearly 600 times normal. (Jakubowska et al., 2002; Jakubowska et al., 2003; Figer et al., 2001).

Some types of infection / inflammation related damage require BRCA1/2 mediated pathways (Figure 1).

Peroxynitrite derived from an inflammatory response produces DNA adducts that require BRCA1/2 and FA dependent homologous recombination for repair. Peroxynitrite oxidizes guanine in DNA producing structures that then react with proteins such as histones or glycosylases to form DNA protein adducts or interstrand cross-links. The lesions are so bulky that BRCA1/2 dependent homologous recombination occurs in preference to nucleotide excision repair (Nakano et al., 2009). Impaired homologous recombination (Figure 1) would thus favor dangerous gene rearrangements if less specific repair methods then operate (Friedenson, 2007; Pace et al., 2010). Another direct correlation is that the BRCA1 associated helicase FA-J (Fig. 1) is required to sense oxidative base damage in either strand of duplex DNA and unwinds the damaged DNA strand. Suhasini et al (2009). Some damage from the alcohol related carcinogen acetaldehyde also depends on specific repairs in Figure 1.

Associations between BRCA1/2, ATM, FA (Fig. 1) and viral cancers or viral proteins

A mutated BRCA1 gene was detected in 13/17 precancerous lesions of the cervix. Park et al (1999). Based on 404 cases of cervical cancer, the BRCA1 variant genotype rs799917 TT was associated with decreased risk of cervical cancer. (OR= 0.62, CI=0.4-0.95). In 469 women with cervical cancer and 390 women with HPV infection, a single nucleotide polymorphism in FA-A was associated with an increased risk for cervical cancer (Wang et al., 2009). FA-F methylation was found in about 30% of 91 cervical cancers (Woodman et al., 2007).

BARD1 (BRCA1 associated ring domain) protein binds to BRCA1, stabilizing both proteins and helping target BRCA1 to sites of DNA damage. BARD1 mutations contribute to some cases of sporadic and hereditary cancers of breast, ovary and uterus (Zhou et al., 2009). BARD1 forms a physical complex with the HPV protein E6 and inactivates the expression of E6 in cervical cancer cells. (Yim et al., 2007). BRCA1 is involved in complex interactions during a response to h. pylori mediated infections (Kim and Kim, 2009).

Infection with HPV activates the ATM-Chk2 checkpoint pathway (Figure 1). This permits repair of damage by homologous recombination (Figure 1) and non-homologous end joining. Not all damaged sites are repaired correctly leading to chromosomal translocations, deletions and rearrangements. Cellular defenses against integrated HPV re-replication are primarily coordinated by ATM. ATM is visualized in the repair and recombination centers of cells infected with HPV. Kadaja et al (2009). An allelic imbalance at chromosome 11q (near or including ATM was found in 34 of 81 cervical cancers (Skomedal et al.,1999).

Reduced activities of BRCA2, FA-J and ATM have been reported in HCV mediated hepatocellular carcinoma compared to normal uninfected cells (Ghaziani et al., 2006; Kondoh et al., 2001; Lai et al., 2008). HCV contains a helicase that interacts with host protein ATM, impairing repair of DNA double strand breaks and cross-links.

Relationship to a DNA interstrand cross-linking carcinogen

Alcohol consumption increases risks for cancers of the upper aerodigestive tract, liver, colorectum, and female breast (Baan et al., 2007). The sites for these cancers are influenced by acetaldehyde a known carcinogen produced during alcohol metabolism. Acetaldehyde generates DNA –protein and interstrand cross-links. The

response to this damage results in a concentration-dependent increase in FA-D2 mono-ubiquitylation, which is dependent upon the FA core complex (Figure 1). The acetaldehyde DNA damage response is qualitatively similar to the cellular response to mitomycin C, the classic test for deficiencies in FA (Marietta et al., 2009). Alcohol also causes oxidative stress, endoplasmic reticulum stress, and inflammatory / immune responses.

Increased risk for pancreatic and prostate cancers.

It is well known that BRCA1 and/or BRCA2 mutation carriers have increased risks for pancreatic and prostate cancers Kim et al., 2009; Agalliu et al., 2009). In normal individuals, chronic inflammation in the target organ predisposes to either cancer. Patients with chronic alcoholic pancreatitis or with familial chronic pancreatitis have much higher incidence of pancreatic carcinoma. Exposure to infectious agents and carcinogens and hormonal imbalances lead to prostate injury, to chronic inflammation and to high risk lesions (De Marzo et al., 2007).

Other cancers with probable links to inflammation strongly correlate with biallelic BRCA2 mutation.

In carriers of compound BRCA2 mutations, risks for other cancers associated with chronic infections and inflammation are very strongly linked to the presence of the mutation. Acute myeloid leukemias of the monocytic lineage can be induced reproducibly and with high incidence due to collaborative effects from severe chronic inflammation and infection by specific retroviruses (Wolff et al., 1991). In 6 children with biallelic BRCA2 mutations, leukemia occurred in all 6 at a median of 2.2 years of age, with 4 of the 6 developing acute myeloid leukemia. Solid tumors with links to inflammation are also extraordinarily frequent. Of 14 patients with biallelic BRCA2 mutations, 5 died of early onset brain tumors, primarily medulloblastomas, and 3 developed Wilms tumors (Wagner et al., 2004). These are all cancers with known links to chronic infection/inflammation. In a formal review of biallelic BRCA2 mutation patients (Alter et al. 2007) similarly found dramatic risks for specific cancers with strong associations to inflammation. Cumulative probability of leukemia (primarily AML) was 79% by age 10 years, that of a solid tumor was 83% by age 6.7 years, that of a brain tumor (primarily medulloblastoma) was 85% by age 9 years, that of a Wilms tumor was 63% by age 6.7 years.

Hereditary colon cancer may involve different inherited genomic deficits but the site for cancer is still dictated by exposure to carcinogens.

Alcohol is causally linked to colon cancer in normal individuals (Baan et al., 2007). Alcohol metabolism produces acetaldehyde which cause damage requiring the Figure 1 pathway for repair. In BRCA1/2 mutation carriers, colon cancer is difficult to detect because the average age of developing colon cancer (70 years) is the same as the life expectancy of a BRCA mutation carrier with mutation diagnosed at age 30 (Armstrong et al., 2004). Very few patients in colon cancer clinics will therefore have BRCA1/2 mutations. Elevated risk for colon cancer has been reported in BRCA1 carriers (Ford et al., 1994). Other studies conflict but Thompson et al. (2002) found enough “digestive tract cancers” or unknown primary cancers to significantly change reported risks for colorectal cancers. Colorectal cancer is difficult to diagnose and is a common cause for primary cancers with unknown origin. Based on a small study, a chromosomal marker near the BRCA1 gene may be a useful marker for identifying genetic instability in ulcerative colitis lesions leading to neoplastic development (Matsumoto et al., 2003).

This gives added importance to colon cancer models that can test for the involvement of Fig. 1. In Atm deficient mice, feeding dextran sulfate induces colitis that clinically and experimentally resembles ulcerative colitis and its progression to colon cancer. Intestinal inflammation causes DNA single- and double-stranded breaks and oxidized bases. Markers of reactive oxygen and nitrogen species–mediated damage, including 8-oxoguanine and nitrotyrosine, were greater in Atm deficient mice than in wild-type mice (Westbrook and Schiestl, 2010). This again shows a carcinogen or mutagen (dextran sulfate) dictating the site for at least a cancer precursor in the presence of a general repair deficit.

The colon comes into relatively prolonged contact with antigens, pathogens and mutagens in the diet. The extent of inflammation and other damage need not correlate with the cancer risk due to BRCA1/2 mutation alone. Inflammation and reactive oxygen species cause a wide variety of damage to DNA including strand breaks, protein cross-linking and base modifications requiring multiple different repair pathways. In addition to BRCA1/2 related pathways, various inflammation damage is repaired by mismatch repair, nucleotide excision repair, base excision repair, transcription coupled repair, etc. More than 20 base lesions alone have been identified due to oxidative DNA damage. The

nature of the lesion is important in dictating the repair process which need not involve BRCA1/2 pathways.

In one form of hereditary colon cancer, a glycosylase enzyme is missing that is needed for excision repair of 8-oxoguanine DNA, a by-product of inflammation in the colon. Inherited defects in this enzyme (MUTYH) allow increases in 8-oxoguanine DNA, (David et al., 2007). In studies of interactions with environmental factors, colon cancer risk for 8-oxoguanine glycosylase genotypes differed depending on dietary exposures such as the amount of meat in the diet (Weiss et al., 2005). This again suggests that the carcinogen (and its route of ingestion or exposure) plays a major role in determining the site for hereditary cancers.

MUTYH cancers are indistinguishable from the hereditary cancer condition familial adenomatous polyposis (FAP) associated with an inherited mutation in the APC gene. The intestinal epithelium becomes littered with hundreds to thousands of polyps, some of which progress to invasive cancers. FAP patients have high risks for other infection/inflammation related cancers (liver, stomach, pancreatic cancers and medullablastoma). Normal intestinal tissue in FAP patients is heterozygous for wild-type APC, but polyps show loss of the wild-type APC allele. APC is essential for beta-catenin signaling, for microtubule plus-end binding and stabilization, for efficient spindle checkpoint activation, and for cytokinesis. How disruption of APC function contributes to tumor progression is poorly understood (Ceol et al., 2007). Specific targeting of hereditary cancers need not occur because of defective repair processes alone. Nonetheless chronic inflammation in the colon exacerbates cancer risks. Anti-inflammatory drugs (NSAIDs) reduce the number and the size of adenomatous polyps.

Heterozygous non-polyposis colon cancer (HNPCC) is associated with an inherited deficit in mismatch repair. A double blind factorial randomized clinical trial studied effects of the anti-inflammatory aspirin in 1,071 carriers HNPCC for a mean period of 51 months. Cancer sufferers in the aspirin group were outnumbered 2 to 1 with a clear effect for duration of treatment (Burn et al., 2009).

Summarizing relative risks from high quality epidemiologic studies of mutation carriers shows that three chronic inflammatory infections greatly increase cancer risks in FA, BRCA1/2 and ATM mutation carriers

Table 1 shows RR data from FA, BRCA1/2 and ATM mutation carriers for five organ specific cancers with well-known associations with chronic infection/ inflammation – cancer of the liver, cervix, vulva, head and neck area, and stomach. For these cancers, the pathogen is an important factor in determining which cancer occurs.

For homozygotes each of three available studies gives very large RR values for cancers of the liver, cervix, vulva and head and neck area. Summary RR values are hundreds of times above control groups (Table 1, top row), with onset accelerated into early ages. (Alter, 2003) For heterozygotes, results summarized in Table 1 show that a deleterious mutation in BRCA1, BRCA2 or ATM genes greatly increases risks for cancers known to be linked to chronic infection.

There are strong precedents for the idea that the same process can be inactivated at multiple points. Cancer genome sequences show that more than one mutation within the same pathway is unusual (Vogelstein and Kinzler, 2004). Other processes such as mismatch repair that depend on multiple genes can be inactivated by inactivating any of several genes encoding proteins within the pathway. The model pathway in Fig. 1 suggests that ATM, BRCA1, BRCA2 and FA genes encode proteins needed to repair DNA damage to specific organs caused by pathogens, inflammation or carcinogens. Models for BRCA repair functions that differ from Figure 1 are still consistent with a role in repairing DNA damage related to pathogens, inflammation, or carcinogens (Cohn and D'Andrea, 2008; Knipscheer et al., 2009; Whitby, 2010; Gari et al., 2008).

Hereditary Cancers are also targeted to breast and ovary by inflammatory processes

Although, investigated by many groups, no pathogens, sources of chronic inflammation or carcinogens have been conclusively linked to breast and ovarian cancer. However there is evidence that these mechanisms operate in hereditary breast and ovarian cancer. The distal fimbrial end of the fallopian tube is an important site for cancer genesis in BRCA1/2 mutation carriers (Hirst et al., 2009; Crum et al., 2007; Callahan et al., 2007; Cass et al., 2005; Demopoulos et al., 2001; Lee et al., 2007).

Tubal ligation protects against ovarian cancer

30 publications show an inverse association between ovarian cancer risk and tubal ligation based on data from hundreds of thousands of women. In mutation carriers, pooled OR = 0.69 (95% CI = 0.55-0.85) for risk of ovarian cancer after tubal ligation. Several studies show that tubal ligation substantially reduces ovarian cancer risk for BRCA1 carriers (McGuire et al., 2004; McGlaughlin et al., 2007; Narod et al., 2001; Rutter et al., 2003). A large study reported HR=0.49 (0.22-0.80) (Antoniou et al., 2009).

Tubal ligation commonly removes sections of tubes between the uterus and fimbria, presumably preventing infection/inflammation from reaching the distal ends. This suggests pathogens, infection/inflammation, or carcinogens must travel through the tube to cause ovarian cancer.

Table 1. Cancer risks linked to chronic inflammatory infections at specific organ targets in cohorts with mutations in FA, BRCA1, BRCA2 and ATM

Genetic inheritance	RR Liver Cancer [95% Confidence Interval]	RR Cervix Cancer [95% Confidence Interval]	RR Stomach Cancer [95% Confidence Interval]	RR Head Neck Cancer [95% Confidence Interval]	References
FA gene homozygotes	478.6 [255.9 - 895.2], I^2=0	193.5 [74.81 - 500.7], I^2= 44%		202.2 [138.0 - 296.4] I^2=0	Alter (2003,) Kutler et al. (2003b), Rosenberg et al (2003)
BRCA1 heterozygotes	4.06 [1.77 - 9.34]	3.84 [2.33 - 6.33]	1.56 [0.91 - 2.68] Peritoneal, intestinal tract" abdomen not otherwise specified" cancers were also found and reported as "other" cancers.	0.15 [0.06 - 0.40] as "buccal cavity and pharynx" cancers. RR=7.40 [5.14-10.66] for "other" cancers including paranasal sinus cancers often originating in the oropharynx	Thompson et al. (2002)
BRCA2 heterozygotes or presumptive	4.18 [1.56 – 11.23], I^2=0	2.26 [0.71 - 7.19], I^2= 42%	2.76 [1.77 - 4.29], I^2=0	2.26 [1.22 - 4.17], I^2=0	Hemminki et al. (2005), Johannsson et al. (1999), Breast Cancer Linkage Consortium (1999)
ATM heterozygotes	3.82 [2.23 - 6.55], I^2=0	3.06 [1.83 - 5.11], Moment based between study variance = 0	3.66 [1.29 – 5.78], I^2= 1.6%		Geoffrey-Perez et al. (2001) Olsen et al. (2005) Swift et al. (1976)
RR Data pooled from heterozygous carriers of mutation in BRCA1, BRCA2 or ATM	3.87 [2.58-5.81], I^2=0	3.14 [2.27 - 4.35], I^2= 1.1%	2.38 [1.64 - 3.45],I^2= 42%	2.26 [1.22 - 4.71] I^2=0% for subgroup (buccal cavity, pharynx or oral cavity)	Thompson et al (2002) Hemminki et al. (2005), Johannsson et al (1999), Breast Cancer Linkage Consortium (1999 Geoffrey-Perez et al (2001) Olsen et al (2005) Swift et al (1976)), Evans et al (2001)

Risks for cancers of the liver, cervix, stomach and head and neck area are shown separately in rows 2-4 for heterozygous mutations in BRCA1, BRCA2 and ATM. In the bottom row these risks are calculated by pooling RR data from BRCA1, BRCA2, probable BRCA1/2 (untyped), and ATM heterozygous carriers. This pooled data includes 24, 272 heterozygotes as19,765 BRCA1/2 heterozygotes or potential heterozygotes and 4507 ATM heterozygotes or potential heterozygotes The effects of different variables on the statistical results and the robustness of the results were measured by performing meta-analyses using many different combinations of studies and study arms. Heterogeneity testing (as I^2 or between study variance) evaluated whether the effect size in different subgroups (defined biologically or medically) varied significantly from the main effect. An I^2 value >50% generally indicates significant heterogeneity (Higgins et al., 2003). For cervical cancer, a possible source of inconsistency may be differences in Pap testing. Stomach cancer may be underestimated in BRCA1 carriers because significant numbers of "abdomen not otherwise specified" as well as peritoneal and intestinal tract cancers were reported by Thompson et al (2002). Moreover, stomach cancer typically occurs late in life and is subject to competing risks. Subgroup analysis suggested RR values and inconsistency in head and neck cancer studies (87.1%) may partly depend on differences in defining head and neck cancers. Three studies reported HNSCC as cancer of the buccal cavity and/or pharynx or oral cavity. A subgroup of these three studies gives a summary RR=2.26 [1.22- 4.17] with 0% inconsistency. However, HPV is most clearly associated with oropharyngeal cancer (63% in the US), arising predominantly from the lingual and palatine tonsils (D'Souza et al., 2007). The one study that specifically reported oropharyngeal cancer also found the highest RR (Evans et al., 2001). Details of these calculations have been reported elsewhere Friedenson (2010) submitted. Briefly, cohorts in the table had a documented mutation in the family and/or numerous breast or other cancers at age <60. Inherited defects were in FA proteins, BRCA1, BRCA2 or the upstream activator ATM. Studies of groups having a known probability of carrying a mutation <25% (3 studies) were excluded. Other exclusion criteria were > 20% of subjects lost due to mortality, illness, refusal to participate, missing information, lost branches of family trees, dropouts, etc. or some other preselection such as ignoring family branches likely to have cancer (7 studies). Any of these criteria would potentially weight results for cancer survivors or people who never get cancer (Friedenson, 2009). No assumptions were made about the risk for a cancer at any individual site unless the study reported incidence at the site. In order to qualify for inclusion, a study had to meet the following a priori criteria of quality. The study had to (1) have sufficient follow-up (1-10 years) (2) include incidence data from >100 individuals for cancers beyond breast and ovarian cancer, (3) have a probability of mutation >=25%, assuming a positive family history (4) provide relative risks for cancers beyond breast and ovarian, with confidence intervals (CIs) or sufficient data to allow calculation of RRs and CIs. A standard protocol was followed to extract data from each included study.

Talc use has been associated with ovarian cancer

It is well known that talc causes inflammation in the pleural cavity. In the past some talc contained asbestos fibers. Talc reaches the upper abdominal cavity and is detected in surgically removed ovaries. RR for ovarian cancer as high as 4.8 (2.1-11) have been reported (Gates et al., 2008). However this risk in mutation carriers has not been studied.

Inhibiting ovulation reduces risk for ovarian cancers.

Ovulation itself may cause inflammation in both the ovary and the fimbria. At the site of ovum release, leukocyte invasion, release of nitric oxide and inflammatory cytokines, vasodilation, DNA repair, and tissue remodeling (resembling wound healing) all occur. (Fleming et al., 2006). Inhibiting ovulation by oral contraceptives (OC) decreases cancer risk in mutation carriers. HR = 0.52; (0.37-0.73; p = 0.0002) for BRCA1 carriers who had ever used OC. Increasing duration of OC use was associated with a reduced ovarian cancer risk in both mutation carriers and in normal women (Antoniou et al., 2009; Siskind et al., 2000)

Tumor infiltrating lymphocytes in hereditary ovarian and breast cancers

Intraepithelial $CD8^+$ T-cells correlated with the presence of mutation or loss of expression of BRCA1 through promoter methylation (Clarke et al., 2009). Macrophages may also be found in ovarian tumors (Fleming et al., 2006).

In normal women, transitions from normal breast to benign proliferative breast disease to ductal carcinoma in situ to infiltrating ductal carcinomas were associated with significantly increased mean densities of inflammatory cell infiltrates. Large increases in infiltrates occur in the precursor form benign proliferative breast disease compared to stroma (Hussein and Hassan, 2006). Breast inflammation as lobulitis was found in 21/41 prophylactic mastectomy specimens from high risk women vs. 8/82 controls (Hermsen et al., 2005). BRCA1/2 mutation carriers have a denser lymphoid infiltrate in breast cancers compared to matched, sporadic control group (Adem et al., 2003). Cancers associated with BRCA1 mutations had more lymphocytic infiltration than sporadic, control cancers (Lakhani et al., 1998; Adem et al., 2003; Lakhani, 1999) and a higher expression of lymphocyte specific genes on microarray analysis (van't Veer et al., 2002). Medullary cancer is more frequent in BRCA1/2 mutation carriers and is also closely associated with a dense lymphocyte infiltrate (Kuroda et al., 2005).

Infection associated gene signature suggests a deregulated immune or inflammatory response to some pathogen

Genes important for immunity to infection and for removal of abnormal cells are over expressed in normal parous women but are not over expressed in BRCA1 carriers (Buckley et al., 2007). BRCA1 expression is essential to up-regulate a group of IFN-gamma controlled genes including an anti-viral protein (8-fold) and an antigen presentation protein (2-fold). 40% of 96 breast cancer samples had a strong signature for an interferon induced pathway (Einav et al., 2005).

Candidate sources for breast carcinogenesis and for infection / inflammation

Alcohol consumption has been causally linked to breast cancer (Baan et al., 2007). Candidate sources for pathogens or infection / inflammation underlying breast cancer include human endogenous retroviruses (HERV). HERV-like sequences are integrated within the human genome. Expression of these sequences can cause inflammatory responses. Strong antibody and T-cell responses to HERV antigens have been found in women with early onset breast cancer and other breast cancer patients. HERV was reactivated in 88% of breast cancer samples including young women at greater risk for BRCA1/2 mutations but not in controls (Wang-Johanning et al., 2008). BRCA1/2 status was not determined but most breast cancers occurred in younger age patients (ages <=55 and < 50) (Wang-Johanning et al., 2008). RNA expression from retrovirus was found in high titer in circulating blood from 20 breast cancer patients (Contreras-Galindo et al., 2008).

Viruses including EBV, a human equivalent of mouse mammary tumor virus (MMTV), and HPV have been detected in benign breast tissues and breast tumors. All are candidate pathogens or sources of infection and inflammation that might give rise to breast cancer. De Villiers et al. (2004) demonstrated the occurrence of HPV in high percentages of nipple and areolar tissues in patients with breast carcinoma but another study disagreed (De Cremoux et al., 2008).

NSAIDs

Anti-inflammatory NSAIDs reduce ovarian cancer risk in nulliparous women when other effect modifiers are corrected. Wernli et al (2008) found OR=0.47(0.27-0.82) for nulliparous women and OR=0.58 (0.42-0.80) for women who had never used oral contraceptives. Five meta-analyses including up to 91 studies, involving millions of subjects comparing NSAID users to non-users

find that NSAIDs protect against breast cancer (Takkouche et al.,2008). In a 2010 study, Brasky et al. found that recent aspirin use was inversely associated with breast cancer risk (adjusted OR 0.80, 95% CI: 0.68-0.94); the greatest reduction in risk occurred among those who took >/=2 aspirin pills/day (OR 0.74, 95% CI: 0.61-0. 90).

NSAID results that specifically address breast cancer risk in BRCA1 or BRCA2 mutation carriers are needed, but there are results from women with a family history of breast cancer. Harris et al (2003) studied NSAID use in 3546 women with a family history of breast cancer as part of the very large Women's Health Initiative (WHI) study. Stratification according to family history is more likely to represent mutation carriers than stratification according to other variables (body mass index, hormone replacement therapy, parity under age 30, or strenuous exercise). After age adjustment or multivariate analyses, women with a family history of breast cancer who used NSAIDs had the greatest apparent reduction in RR. However confidence intervals overlapped other strata (Harris et al., 2003).

CONCLUSION

Mutations in BRCA1/2 genes and other hereditary mutations increase cancer risks from chronic infection, inflammation pathogens and at least one carcinogen which contribute to selecting the site where hereditary cancer develops. This information may be useful to prevent or delay cancers in mutation carriers.

ACKNOWLEDGEMENT

This work was supported by a grant from the University of Illinois Chicago.

REFERENCES

Adem C, Reynolds C, Soderberg CL, Slezak JM, McDonnell SK, Sebo TJ, Schaid DJ, Myers JL, Sellers TA, Hartmann LC, Jenkins RB (2003). Pathologic characteristics of breast parenchyma in patients with hereditary breast carcinoma, including BRCA1 and BRCA2 mutation carriers. Cancer 97: 1-11.

Agalliu I, Gern R, Leanza S, Burk RD(2009). Associations of high-grade prostate cancer with BRCA1 and BRCA2 founder mutations. Clin Cancer Res. 15(3):1112-20.

Alter B (2003). Cancer in Fanconi Anemia, 1927–2001. Blood 97: 425-440.

Alter B, Rosenberg P, Brody L. (2007). Clinical and molecular features associated with biallelic mutations in FANCD1/BRCA2 J Med Genet. 44:1–9.

Antoniou A, Rookus M, Andrieu N, Brohet R, Chang-Claude J. (2009). Reproductive and hormonal factors, and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: results from the International BRCA1/2 Carrier Cohort Study. Cancer Epidemiol. Biomarkers Prev. 18: 601-10.

Armstrong K, Schwartz S, Randal T, Rubin S, Weber B. (2004) Hormone Replacement Therapy and Life Expectancy After Prophylactic Oophorectomy in Women With BRCA1/2 Mutations: A Decision Analysis. J. Clin Oncol. 22(6):1045-1054

Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Altieri A, Cogliano V; WHO International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of alcoholic beverages (2007). Lancet Oncol. 8(4):292-3.

Baldridge M, King K, Boles N, Weksberg D, Goodell M (2010). Quiescent haematopoietic stem cells are activated by IFN-γ in response to chronic infection. Nature 465: 793-797

Bolderson E, Tomimatsu N, Richard D, Boucher D, Kumar R, Pandita T, Burma S, Khanna K (2010). Phosphorylation of Exo1 modulates homologous recombination repair of DNA double strand breaks. Nucl Acids Res 38: 1821-1831.

Brasky T, Bonner M, Moysich K, Ambrosone C, Nie J, Tao M, Edge S, Kallakury B, Marian C, Trevisan M, Shields P, Freudenheim J. (2010) Non-steroidal anti-inflammatory drug (NSAID) use and breast cancer risk in the Western New York Exposures and Breast Cancer (WEB) Study. Cancer Causes Control. 2010 May 25.

Buckley NE, Hosey AM, Gorski JJ, Purcell JW, Mulligan JM, Harkin DP, Mullan PB (2007). BRCA1 regulates IFN-γ signaling through a mechanism involving type 1 IFNs. Molec Cancer Res. 5: 261-70.

Burn J, Mathers JC, Gerdes AM, et al. (2009) Cancer occurrence during follow-up of the CAPP2 study—aspirin use for up to 4 years significantly reduces Lynch syndrome cancers for up to10 years. Available from: URL http://www.capp2.com/newsZone/readnews.php?NewsID=45

Callahan MJ, Crum CP, Medeiros F, Kindelberger DW, Elvin JA, Garber JE, Feltmate CM, Berkowitz RS, Muto MG (2007). Primary Fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. J. Clin. Oncol.. 25: 3985-90.

Cass I, Holschneide C, Datta N, Barbuto D, Walts A, Karlan B. (2005). BRCA-mutation-associated fallopian tube carcinoma. A distinct clinical phenotype. Obstet. Gynecol. 106: 1327-1334.

Ceol CJ, Pellman D, Zon LI. (2007). APC and colon cancer: two hits for one. Nat Med. 13(11):1286-7.

Clarke B, Tinker AV, Lee CH, Subramanian S, van de Rijn M, Turbin D, Kalloger S, Han G, Ceballos K, Cadungog MG, Huntsman DG, Coukos G, Gilks CB (2009) Intraepithelial T cells and prognosis in ovarian carcinoma: novel associations with stage, tumor type, and BRCA1 loss. Modern Pathol. 22: 393-402.

Cohn M and D'Andrea A (2008). Chromatin Recruitment of DNA Repair Proteins: Lessons from the Fanconi Anemia and Double-Strand Break Repair Pathways. Molec. Cell 32: 306-312.

Contreras-Galindo R, Kaplan MH, Leissner P, Verjat T, Ferlenghi I, Bagnoli F, Giusti F, Dosik MH, Hayes DF, Gitlin SD, Markovitz DM. (2008). Human Endogenous Retrovirus K (HML-2) Elements in the plasma of people with lymphoma and breast Cancer. J. Virol. 82: 9329–9336.

Crum C, Drapkin R, Kindelberger D, Medeiros F, Miron A, Lee Y (2007). Lessons from BRCA: the tubal fimbria emerges as an origin for pelvic serous cancer. Clin. Med. & Res. 5: 35-44,

D'Andrea A, Grompe M (2003). The Fanconi anaemia/BRCA pathway. Nature Rev. Cancer 3: 23-34.

David SS, O'Shea VL, Kundu S. (2007) Base-excision repair of oxidative DNA damage. Nature. 447(7147):941-50.

de Cremoux P, Thioux M, Lebigot I, Sigal-Zafrani B, Salmon R, Sastre-Garau X; Institut Curie Breast Group (2008). No evidence of human papillomavirus DNA sequences in invasive breast carcinoma. Breast Cancer Res Treat. 109(1):55-8.

De Marzo AM, Platz EA, Sutcliffe S, Xu J, Grönberg H, Drake CG, Nakai Y, Isaacs WB, Nelson WG (2007). Inflammation in prostate carcinogenesis. Nature Rev. Cancer 7: 256-269.

Demopoulos R, Aronov R, Mesia A. (2001). Clues to the Pathogenesis of Fallopian Tube Carcinoma: A Morphological and Immunohistochemical Case Control Study, Internat. Journal of Gynecol. Pathol. 20: 128–132.

DerSimonian R, Laird N (1986). Meta-Analysis in clinical trials. Controlled Clin. Trials 7: 177-188.

de Villiers EM, Sandstrom RE, zur Hausen H, Buck CE (2005). Presence of papillomavirus sequences in condylomatous lesions of the mamillae and in invasive carcinoma of the breast. Breast Cancer Res .7(1):R1-11.

Dizin E, Irminger-Finger I (2010). Negative feedback loop of BRCA1-BARD1 ubiquitin ligase on estrogen receptor alpha stability and activity antagonized by cancer-associated isoform of BARD1. Int J Biochem Cell Biol. 42(5):693-700.

D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML. (2007). Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med. 356(19):1944-56.

Einav U, Tabach Y, Getz G, Yitzhaky A, Ozbek U, Amariglio N, Izraeli S, Rechavi G, Domany E (2005). Gene expression analysis reveals a strong signature of an interferon induced pathway in childhood lymphoblastic leukemia as well as in breast and ovarian cancer. Oncogene. 24: 6367-6375,.

Evans H, Lewis C, Robinson D, Bell C, Møller H, Hodgson S. (2001). Cancer risks in women with 2 breast or ovarian cancers: clues to genetic susceptibility. Internat. J. Cancer. 94: 758-9.

Fan, S., Ma, Y.X., Wang, C., Yuan, R.Q., Meng, Q., Wang, J.A., Erdos, M.,Goldberg, I.D., Webb, P., Kushner, P.J., et al. (2001). Role of direct interactionin BRCA1 inhibition of estrogen receptor activity. Oncogene 20: 77–87.

Figer A, Irmin L, Geva R, Flex D, Sulkes J, Sulkes A, Friedman F (2001). The rate of the 6174delT founder Jewish mutation in BRCA2 in patients with non-colonic gastrointestinal tract tumours in Israel. Brit. J. Cancer 84: 478-81.

Fleming J, Beaugie C, Haviv I, Chenevix-Trench G, Tan O (2006). Incessant ovulation and epithelial ovarian carcinogenesis: revisiting old hypotheses. Mol. Cell Endocrinol. 247: 4-21.

Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE.(1994). Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet. 343(8899):692-5.

Friedenson B (2007). The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC Cancer. 7, pp. 152-ff.

Friedenson B (2009). DEWEY DEFEATS TRUMAN and cancer statistics. J. Natl Cancer Inst. 101, no.16, 1157.

Gardner K, Liu E.(2001). BRCA1 function in T lymphocytes: a cellular specificity of a different kind. Breast Cancer Res 3:11-13.

Gari K, Décaillet C, Stasiak A, Stasiak A, Constantinou A (2008). The Fanconi Anemia Protein FANCM Can Promote Branch Migration of Holliday Junctions and Replication Forks. Molec. Cell, 29: 141-148

Gates MA, Tworoger SS, Terry KL, Titus-Ernstoff L, Rosner B, De Vivo I, Cramer DW, Hankinson SE (2008). Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. Cancer Epidemiol. Biomarkers Prev. 17: 2436-44.

Geoffroy-Perez B, Janin N, Ossian K, Laugé A, Croquette MF, Griscelli C, Debré M, Bressac-de-Paillerets B, Aurias A, Stoppa-Lyonnet D, Andrieu N (2001). Cancer risk in heterozygotes for ataxia-telangiectasia. Internat. J. Cancer 93: 288-293.

Ghaziani T, Shan Y, Lambrecht R, Donohue S, Pietschmann T, Bartenschlager R, Bonkovsky H. (2006). HCV proteins increase expression of heme oxygenase-1 (HO-1) and decrease expression of Bach1 in human hepatoma cells. J. Hepatology 45: 5-12.

Golan E, Korzets Z, Cristal-Lilov A, Ben-Tovim T, Bernheim J. (1996). Increased prevalence of HCV antibodies in dialyzed Ashkenazi Jews--a possible ethnic predisposition. Nephrology Dialysis Transplantion 11: 684-6.

Gompel, A., Somai, S., Chaouat, M., Kazem, A., Kloosterboer, H.J.,Beusman, I., Forgez, P., Mimoun, M., Rostene, W. (2000). Hormonal regulation of apoptosis in breast cells and tissues. Steroids 65: 593–598.

Hadjur S, Ung K, Wadsworth L, Dimmick J, Rajcan-Separovic E, Scott RW, Buchwald M, Jirik FR (2001). Defective hematopoiesis and hepatic steatosis in mice with combined deficiencies of the genes encoding Fancc and Cu/Zn superoxide dismutase. Blood 98:1003-11.

Harris RE, Chlebowski RT, Jackson RD, Frid DJ, Ascenseo JL, Anderson G, Loar A, Rodabough R, White E, McTiernan A; Women's Health Initiative (2003). Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative. Cancer Res. 63(18):6096-101.

Hemminki K, Scélo G, Boffetta P, Mellemkjaer L, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride M, Kliewer EV, Chia KS, Pompe-Kirn V, Martos C, Jonasson JG, Li X, Brennan P (2005). Second primary malignancies in patients with male breast cancer. Brit. J. Cancer 92 : 1288-92.

Hermsen B, von Mensdorff-Pouilly S, Fabry H, Winters H, Kenemans P, Verheijen R, van Diest P (2005). Lobulitis is a frequent finding in prophylactically removed breast tissue from women at hereditary high risk of breast cancer. J. Pathol. 206: 220-3.

Higgins J, Thompson S, Deeks J, Altman D. (2003). Measuring inconsistency in meta-analyses. Brit. Medical Journal 327: 557-60.

Hirst JE, Gard GB, McIllroy K, Nevell D, Field M (2009). High rates of occult fallopian tube cancer diagnosed at prophylactic bilateral salpingo-oophorectomy. Int J Gynecol Cancer19(5): 826-9.

Hussein M, Hassan H (2006). Analysis of the mononuclear inflammatory cell infiltrate in the normal breast, benign proliferative breast disease, in situ and infiltrating ductal breast carcinomas: preliminary observations. J. Clin. Pathol. 59: 972–977.

Jakubowska A, Nej K, Huzarski T, Scott R, Lubiński J (2002). BRCA2 gene mutations in families with aggregations of breast and stomach cancers. Brit. J. Cancer 87: 888-91.

Jakubowska A, ScottR, Menkiszak J, et al. (2003). A high frequency of BRCA2 gene mutations in Polish families with ovarian and stomach cancer. European J. Human Genet. 11: 955-8.

Johannsson O, Loman N, Moller T, Kristoffersson U, Borg A, Olsson H (1999) Incidence of malignant tumours in relatives of BRCA1 and BRCA2 germline mutation carriers. European J. Cancer. 35, pp. 1248-1257.

Joosse S, van Beers E, Tielen I, Hugo Horlings H, Peterse J, Hoogerbrugge N, Ligtenberg M, Wessels L, Axwijk P, Verhoef S, Hogervorst F, Nederlof P (2009). Prediction of BRCA1-association in hereditary non-BRCA1/2 breast carcinomas with array-CGH. Breast Cancer Res Treat 116:479–489

Jönsson G, Naylor TL, Vallon-Christersson J, Staaf J, Huang J, Ward MR, Greshock JD, Luts L, Olsson H, Rahman N, Stratton M, Ringnér M, Borg A, Weber BL. (2005). Distinct genomic profiles in hereditary breast tumors identified by array-based comparative genomic hybridization. Cancer Res.65(17):7612-21.

Kadaja M, Isok-Paas H, Laos T, Ustav E, Ustav M (2009). Mechanism of genomic instability in cells infected with the high-risk human papillomaviruses. PLoS Pathog. 5(4):e1000397.

Kim DH, Crawford B, Ziegler J, Beattie MS (2009). Prevalence and characteristics of pancreatic cancer in families with BRCA1 and BRCA2 mutations. Fam Cancer. 8(2):153-8.

Kim KK, Kim HB. (2009). Protein interaction network related to Helicobacter pylori infection response. World J Gastroenterol. 15(36):4518-28.

King M-C, Marks J, Mandell, J (2003). Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 302: 643 – 646.

King M-C, Wieand S, Hale K, et al. (2001). National Surgical Adjuvant Breast and Bowel Project, Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA 286: 2251-6.

Knipscheer P, Räschle M, Smogorzewska A, Enoiu M, Ho TV, Schärer OD, Elledge SJ, Walter JC (2009). The Fanconi anemia pathway promotes replication-dependent DNA interstrand cross-link repair. Science 326(5960):1698-701

Kondoh N, Wakatsuki T, Hada A, Shuda M, Tanaka K, Arai M, Yamamoto M (2001). Genetic and epigenetic events in human hepatocarcinogenesis. Internat. J. Oncol. 18: 1271-8.

Kohno H, Takahashi M, Yasui Y, Suzuki R, Miyamoto S, Kamanaka Y, Naka M, Maruyama T, Wakabayashi K, Tanaka T. (2007) A specific inducible nitric oxide synthase inhibitor, ONO-1714 attenuates inflammation-related large bowel carcinogenesis in male Apc(Min/+) mice. Int J Cancer. 121(3):506-13.

Kuroda H, Tamaru J-I, Sakamoto G,. Ohnisi K, Itoyama S (2005). Immunophenotype of lymphocytic infiltration in medullary carcinoma of the breast. Virchows Archives vol. 446: 10-14.

Kutler DI, Auerbach AD, Satagopan J, Giampietro PF, Batish SD, Huvos AG, Goberdhan A, Shah JP, Singh B (2003a). High incidence of head and neck squamous cell carcinoma in patients with Fanconi anemia. Archives of Otolaryngology and Head and Neck Surgery 129: 106-112.

Kutler D, Singh B, Satagopan J, Batish SD, Berwick M, Giampietro PF, Hanenberg H, Auerbach AD. (2003b). A 20-year perspective on the International Fanconi Anemia Registry (IFAR). Blood 101: 1249-56.

Lai C, K. Jeng, K. Machida, Cheng Y, Lai M (2008). Hepatitis C virus NS3/4A protein interacts with ATM, impairs DNA repair and enhances sensitivity to ionizing radiation. Virology 370: 295-309.

Lakhani SR (1999). The pathology of familial breast cancer. Morphological aspects. Breast Cancer Research http://breast-cancer-research.com/vol1no1/27oct99/review/2

Lakhani SR, Jacquemier J, Sloane JP, Gusterson BA, Anderson TJ, van de Vijver MJ, Farid LM, Venter D, Antoniou A, Storfer-Isser A, Smyth E, et al. (1998) Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. J. Natl Cancer Inst. 90: 1138-1145.

Lee Y, A. Miron, R. Drapkin, et al (2007). A candidate precursor to serous carcinoma that originates in the distal fallopian tube. J. Pathol. 211: 26-35.

Lembo D, Donalisio M, Cornaglia M, Azzimonti B, Demurtas A, Landolfo S. (2006).Effect of high-risk human papillomavirus oncoproteins on p53R2 gene expression after DNA damage. Virus Res. 122(1-2):189-93.

Lin C, Yang L, Tanasa B, Hutt K, Ju BG, Ohgi K, Zhang J, Rose DW, Fu XD, Glass CK, Rosenfeld MG (2009). Nuclear receptor-induced chromosomal proximity and DNA breaks underlie specific translocations in cancer. Cell 139: 1069-83.

Liu J, Poiley J, Devetten M, Kajigaya S, Walsh C (1996). The Fanconi anemia complementation group C gene (FAC) suppresses transformation of mutant fibroblasts by the SV40 virus. Biochemical and Biophysical Res. Communications 223: 685-690.

Machado AM, Figueiredo C, Touati E, Máximo V, Sousa S, Michel V, Carneiro F, Nielsen FC, Seruca R, Rasmussen LJ. (2009) Helicobacter pylori infection induces genetic instability of nuclear and mitochondrial DNA in gastric cells. Clin Cancer Res. 15(9):2995-3002.

Machida K, Cheng K, Lai C-K, Jeng K, Sung V, Lai M (2006). Hepatitis C virus triggers mitochondrial permeability transition with production of reactive oxygen species, leading to DNA damage and STAT3 activation. J. Virology 80: 7199-7207.

Marietta C, Thompson LH, Lamerdin JE, Brooks PJ. (2009). Acetaldehyde stimulates FANCD2 monoubiquitination, H2AX phosphorylation, and BRCA1 phosphorylation in human cells in vitro: implications for alcohol-related carcinogenesis. Mutat Res. 664(1-2):77-83.

Matsumoto N, Yoshida T, Okayasu I (2003). High Epithelial and Stromal Genetic Instability of Chromosome 17 in Ulcerative Colitis-associated Carcinogenesis. Cancer res 63: 6158–6161

McLaughlin JR, Risch HA, Lubinski J, Moller P, Ghadirian P, Lynch H, Karlan B, Fishman D, Rosen B, Neuhausen SL, et al. (2007). Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet Oncol. 8: 26–34.

McGuire V, Felberg A, Mills M, Ostrow KL, DiCioccio R, John EM, West DW, Whittemore AS. (2004). Relation of contraceptive and reproductive history to ovarian cancer risk in carriers and noncarriers of BRCA1 gene mutations. Amer. J. Epidemiology 160: 613-8.

Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF (1999). Improving the quality of reports of meta-analyses of randomised controlled trials: The QUORUM statement. Lancet 354: 1896-1900.

Nakano T, Katafuchi A, Matsubara M, Terato H, Tsuboi T, Masuda T, Tatsumoto T, Pack SP, Makino K, Croteau DL, Van Houten B, Iijima K, Tauchi H, Ide H (2009). Homologous recombination but not nucleotide excision repair plays a pivotal role in tolerance to DNA-protein crosslinks in mammalian cells. J. Biol. Chem. 284: 27065-76.

Narod S, Sun P, Ghadirian P, et al. (2001). Tubal ligation and risk of ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet 357:1467–70.

Olsen JH, Hahnemann JM, Børresen-Dale AL, Tretli S, Kleinerman R, Sankila R, Hammarström L, Robsahm TE, Kääriäinen H, Bregård A, Brøndum-Nielsen K, Yuen J, Tucker M (2005). Breast and other cancers in 1445 blood relatives of 75 Nordic patients with ataxia-telangiectasia. Brit. J. Cancer 93: 260-5.

Pace P, mosedale G. Hodskinson M, Rosado I, Sivrasubramanian M, Patel K. Ku70 Corrupts DNA Repair in the Absence of the Fanconi Anemia Pathway (2010) Science 329: 219-223.

Park S, Chan P, Seraj I, King A (1999). Denaturing gradient gel electrophoresis screening of the BRCA1 gene in cells from precancerous cervical lesions. J. Reproductive Med. 44: 575-80.

Rebbeck T, Kauff N, Domchek S (2009). Meta-analysis of risk reduction estimates associated with risk-reducing salpingooophorectomy in BRCA1 or BRCA2 mutation carriers. J. Natl Cancer Inst. 101: 80 – 87.

Rosen EM, Fan S, Ma Y. (2006). BRCA1 regulation of transcription. Cancer Lett. 236(2):175-85.

Rosenberg P, Greene M, Alter B (2003). Cancer incidence in persons with Fanconi anemia. Blood 101: 822-826.

Rosselli F, Sanceau J, Gluckman E, Wietzerbin J, Moustacchi E. (1994). Abnormal lymphokine production: a novel feature of the genetic disease Fanconi anemia. II. In vitro and in vivo spontaneous overproduction of tumor necrosis factor alpha. Blood 83: 1216–1225.

Rutter J, Wacholder S, Chetrit A, et al. (2003). Gynecologic surgeries and risk of ovarian cancer in women with BRCA1 and BRCA2 Ashkenazi founder mutations: an Israeli population-based case-control study. J. Natl Cancer Inst. 95: 1072–8.

Saito H, Hammond AT, Moses RE (1993). Hypersensitivity to oxygen is a uniform and secondary defect in Fanconi anemia cells. Mutat Res. 294:255-62.

Sawa T, Ohshima H (2006). Nitrative DNA damage in inflammation and its possible role in carcinogenesis. Nitric Oxide 14(2):91-100.

Scully R, Livingston DM. (2000) In search of the tumour-suppressor functions of BRCA1 and BRCA2. Nature. 408(6811):429-32.

Sejas DP, Rani R, Qiu Y, Zhang X, Fagerlie SR, Nakano H, Williams DA, Pang Q (2007). Inflammatory reactive oxygens species-mediated hematopoietic suppression in Fancc-deficient mice. J. Immunol: 178, 5277-5287.

Siskind, V., Green, A., Bain, C., Purdie, D (2000). Beyond ovulation: oral contraceptives and epithelial ovarian cancer. Epidemiology 11: 106–110.

Skomedal H, Helland A, Kristensen G, Holm R, Børresen-Dale A. (1999). Allelic imbalance at chromosome region 11q23 in cervical carcinomas. Eur. J. Cancer 35: 659-63.

Smoot DT, Elliott TB, Verspaget HW, Jones D, Allen CR, Vernon KG, Bremner T, Kidd LC, Kim KS, Groupman JD, Ashktorab H (2000). Influence of Helicobacter pylori on reactive oxygen-induced gastric epithelial cell injury. Carcinogenesis. 21(11):2091-5.

Suhasini A, Sommers J, Mason A, Voloshin O, Camerini-Otero R, Wold M. Brosh R, Jr. (2009). FANCJ helicase uniquely senses oxidative base damage in either strand of duplex DNA and is stimulated by replication protein A to unwind the damaged DNA substrate in a strand-specific manner. J. Biol. Chem. 284: 18458–18470.

Swift M, Sholman L, Perry M, Chase C, (1976). Malignant neoplasms in the families of patients with ataxia-telangiectasia. Cancer Res. 36: 209-15.

Takkouche B, Regueira-Méndez C, Etminan M (2008). Breast cancer and use of nonsteroidal anti-inflammatory drugs: a meta-analysis. J. Natl Cancer Inst. 100: 1439-47.

The Breast Cancer Linkage Consortium (1999). Cancer risks in BRCA2 mutation carriers. J. Natl Cancer Inst. 91: 1310-1316.

Thompson D, Easton D, the Breast Cancer Linkage Consortium (2002). Cancer Incidence in BRCA1 mutation carriers. J. Natl. Cancer Inst. 94:1358-1365.

van 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, Peterse HL, van der Kooy K, Marton MJ, Witteveen AT, Schreiber GJ, Kerkhoven RM, Roberts C, Linsley PS, Bernards R, Friend SH (2002). Gene expression profiling predicts clinical outcome of breast cancer. Nature 415: 530-6.

Venkitaraman A (2003). A growing network of cancer-susceptibility genes. N. Engl. J. Med. 348: 1917-9,

Vogelstein B, Kinzler K (2004). Cancer genes and the pathways they control. Nature Medicine 10: 789-799.

Wagner J, Tolar J, Levran O, Scholl T, Deffenbaugh A, Satagopan J, Ben-Porat L, Mah K, Batish S, Kutler D, MacMillan M, Hanenberg H, Auerbach A. (2004) Germline mutations in BRCA2: shared genetic

susceptibility to breast cancer, early onset leukemia, and Fanconi anemia. Blood. 103:3226-3229

Wang-Johanning F, Radvanyi L, Rycaj K, Plummer JB, Yan P, Sastry KJ, Piyathilake CJ, Hunt KK, Johanning GL. (2008) Human endogenous retrovirus K triggers an antigen-specific immune response in breast cancer patients. Cancer Res. 68: 5869-77.

Wang SS, Bratti MC, Rodríguez AC, Herrero R, Burk RD, Porras C, González P, Sherman ME, Wacholder S, Lan ZE, Schiffman M, Chanock SJ, Hildesheim A (2009). Common variants in immune and DNA repair genes and risk for human papillomavirus persistence and progression to cervical cancer. J Infect Dis. 199(1):20-30.

Ward A, Olive P, Burr A, Rosin M (1994). Response of fibroblast cultures from ataxia-telangiectasia patients to reactive oxygen species generated during inflammatory reactions. Environ. Molec. Mutagenesis 24: 103-11.

Ward A and Rosin M (1993). A protective effect of chromosome 11 against DNA damage by TPA activated neutrophils but not TPA acting alone. Carcinogenesis 15: 2851-7.

Weiss JM, Goode EL, Ladiges WC, Ulrich CM. (2005). Polymorphic variation in hOGG1 and risk of cancer: a review of the functional and epidemiologic literature. Mol Carcinog. 2005 Mar;42(3):127-41.

Welcsh PL, King MC. (2001). BRCA1 and BRCA2 and the genetics of breast and ovarian cancer. Hum Mol Genet. 10(7):705-13.

Wernli K, Newcomb P, Hampton J, Trentham-Dietz A, Egan K. (2008). Inverse association of NSAID use and ovarian cancer in relation to oral contraceptive use and parity. Brit. J. Cancer. 98:1781-1783.

Westbrook A, Schiestl R (2010) Atm-Deficient Mice Exhibit Increased Sensitivity to Dextran Sulfate Sodium–Induced Colitis Characterized by Elevated DNA Damage and Persistent Immune Activation. Cancer Res. 70:1875-1884.

Whitby M (2010). The FANCM family of DNA helicases / translocases. DNA Repair 9: 224–236.

Wolff L, Koller R, Davidson W. (1991) Acute myeloid leukemia induction by amphotropic murine retrovirus (4070A): clonal integrations involve c-myb in some but not all leukemias.. J. Virol. 65(7):3607-3616.

Woodman CB, Collins SI, Young LS. (2007). The natural history of cervical HPV infection: unresolved issues. Nat. Rev. Cancer. 7(1):11-22

Yim EK, Lee KH, Myeong J, Tong SY, Um SJ, Park JS. (2007) Novel interaction between HPV E6 and BARD1 (BRCA1-associated ring domain 1) and its biologic roles. DNA Cell Biol. 26(10):753-61.

Zanier R, Briot D, Dugas du Villard J, Sarasin A, Rosselli F (2004) Fanconi anemia C gene product regulates expression of genes involved in differentiation and inflammation. Oncogene 23; 5004-13.

Zhou B, Elledge S (2002) The BRCA1 suppressor hypothesis:An explanation for the tissue-specific tumor development in BRCA1 patients Cancer Cell 1:129-132.

Zhou X, Han S, Wang S, Chen X, Dong J, Shi X, Xia Y, Wang X, Hu Z, Shen H (2009). Polymorphisms in HPV E6/E7 protein interacted genes and risk of cervical cancer in Chinese women: a case-control analysis. Gynecol Oncol. 114(2):327-31.