

Full Length Research Paper

Inflammatory processes inordinately increase tissue specific cancer risks in carriers of mutations in BRCA1, BRCA2, ATM or Fanconi anemia genes

Bernard Friedenson

Department of Biochemistry and Molecular Genetics, College of Medicine, University Illinois Chicago, 900 South Ashland Ave, Chicago, IL 60607. Email: molmeddoc@gmail.com; Phone /fax 847-298-1641

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It is not known why some inherited cancer gene mutations seem to cause cancer only in certain characteristic organs. Women who inherit a defective BRCA1 or BRCA2 gene inherit risks for breast and ovarian cancer that seem so specific and so high that some carriers have prophylactic surgery. To find other preventive options, this analysis investigated whether chronic infections and inflammation target breast and ovary for inherited cancers. Risks for cancers with well-known links to chronic infection and inflammation were statistically evaluated for carriers of mutations in BRCA1/2 or in related proteins from published studies. Summary risks for known infection/inflammation related cancers were hundreds of times above controls for homozygotes and up to over four times above controls for heterozygotes. Evidence was also found supporting the idea that inflammation targets breast and ovary for hereditary cancers. For example, inflammation precedes hereditary breast cancers; is more pronounced in hereditary breast cancers vs. sporadic breast cancers; accompanies transitions from benign to malignant breast disease; but blocking inflammation reduces these risks. It is well known that chronic inflammation is associated with cancer. A new finding here is that cancer risks from chronic inflammation are inordinately increased in those inheriting a mutation that disables BRCA1, BRCA2, or related proteins. These increased risks can be so large that the tissue specificity for infection or inflammation effectively determines the site for cancer. This gives added importance to research identifying inflammatory processes in mutation carriers. Limiting chronic infections and inflammation may delay or prevent some hereditary cancers.

Keywords: BRCA1, BRCA2, inflammation, ovarian cancer, breast cancer, infection, hereditary cancer.

INTRODUCTION

Women who inherit a defective BRCA1 or BRCA2 gene have risks for breast and ovarian cancer that are so high and apparently so selective that many mutation carriers choose to have prophylactic surgery (Ford et al., 1998;

King et al., 2003; Antoniou et al., 2006; Struewing et al., 1997; Rebbeck et al., 2009; King et al., 2001). This is because a positive test result for a cancer related mutation leaves carriers with very limited options.

ABBREVIATIONS

A-T-ataxia-telangiectasia; ATM-gene mutated in ataxia-telangiectasia
CI-confidence interval;DSB-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; I²-inconsistency statistic
NCI-National Cancer Institute; NK cells-natural killer cells
NSAIDs,-non-steroidal anti-inflammatory drugs; OR-odds ratio;
RR- relative risk; ss DNA- single strand
SEER-surveillance epidemiology and end results

In order to delay or prevent BRCA1/2 related cancers, it may be important to understand why they seem to occur only in certain characteristic organs. Why would cancer just attack breasts and ovaries when every cell with a nucleus contains the same mutation? Functionally, both BRCA genes are general cell requirements because they encode products essential for DNA repairs, checkpoint controls, and other activities. How does inheritance of a defect in general cell requirements lead to cancers in specific target organs?

Here, mutation carriers were found to have inordinately increased risks for cancers connected to known chronic inflammatory infections such as liver cancer, cervical cancer and stomach cancer. Risks

increased hundreds of times in homozygotes and up to over four-fold in heterozygotes. These increases can be so large that the site of infection or inflammation can effectively determine the site for cancer. For BRCA1/2 related breast and ovarian cancers, cancer prevention data and evidence of immune responses suggested that chronic inflammation helps target these organs. This gives added importance to research identifying inflammatory processes in hereditary cancer. Identifying and controlling chronic infections and inflammation may delay or prevent some hereditary cancers in mutation carriers.

MATERIALS AND METHODS

Identification of studies, Construction of a testable model for BRCA1 and BRCA2 function

A working model was constructed for BRCA1/2 function which includes other interconnected proteins based on extensive literature review. The model was derived from PubMed and Google Scholar databases. These databases were systematically searched up to the current date for original studies of BRCA1 and BRCA2 function and to other proteins, required for BRCA1/2 activities. With the model available, subsequent searches were for infection / inflammation related cancers vs. any defect in the model for BRCA1/2 function. 1250 articles published in the past 50 years were retrieved and copied to a database to facilitate further searching. Many bibliographies were also reviewed for additional relevant references that may have been missed. No language restrictions were imposed. In order to reduce bias, explicit procedures were used to systematically identify, appraise, summarize and statistically aggregate relevant epidemiologic studies (Moher et al., 1999).

Examples of cancers with known links to chronic inflammation

From these initial surveys, results were summarized for five cancers that have widely accepted and well-known links to chronic infection as follows. Group 1: liver cancer associated with viral hepatitis such as hepatitis B or C; 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*.

Included research articles analyzed

Comparatively few publications describe cancer histories at sites other than breast or ovary from typed or probable mutation carriers. No studies are available that directly determine the mutation status of every member of a large cohort of non-breast/non-ovarian cancer cases. Therefore, cohorts likely to have a mutation were included based on one or more risk factors for inheriting a mutation in the model pathway (Figure 1) containing BRCA1/2 proteins (Table 1 legend).

When necessary, probability of mutation was estimated using the BRAC analysis risk calculator from Myriad Genetics.

Multi-variate and subgroup analyses

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.

RESULTS

Figure 1 shows a derived model for BRCA1 and BRCA2 in pathways required to repair DNA interstrand cross-links, double strand breaks and to restart stalled replication forks (Venkitarman, 2003; D'Andrea and Grompe, 2002; Bolderson et al., 2010). These repairs require ATM, Fanconi anemia (FA) proteins and BRCA1/2. Although originally pictured as a single process as in Figure 1, the model probably represents the sum of complex pathways that respond to different types of DNA damage.

In support of the model in Figure 1, existing evidence suggests that some losses of these gene products lead to phenotypic similarities. Hereditary conditions due to inactivation of ATM, FA genes, or BRCA1/2 genes all show large chromosomal rearrangements, chromosome breaks and losses or gains of sections of chromosomes. FA cells have a defect in repairing chromosomal and extra-chromosomal double strand breaks, repairs which are generally regarded as requiring BRCA1/ BRCA2 mediated homologous recombination. Abnormal chromosome structures ("radials") from a mouse BRCA2 model closely resemble those from FA patients. Mutated genes encoding proteins in the model in Figure 1 or in detailed models have been designated as "breast" or "ovarian cancer genes." Mutation virtually anywhere in the pathway that can be tested greatly increases risks for a subset of lymphomas and leukemias (Friedenson, 2007). 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).

RR data for 5 cancer associated infection groups, each causing cancer in specific organs

The existence of hereditary diseases involving genes related to Fig. 1 has led to epidemiologic studies that measure cancer risks in populations of mutation carriers. Ataxia-telangiectasia (A-T) and Fanconi anemia (FA) are inherited diseases with homozygous inactivation of the ATM gene and one of at least 13 FA genes, respectively. Cancer epidemiology statistics for A-T, FA and from BRCA1/2 mutation carriers were used to test whether the

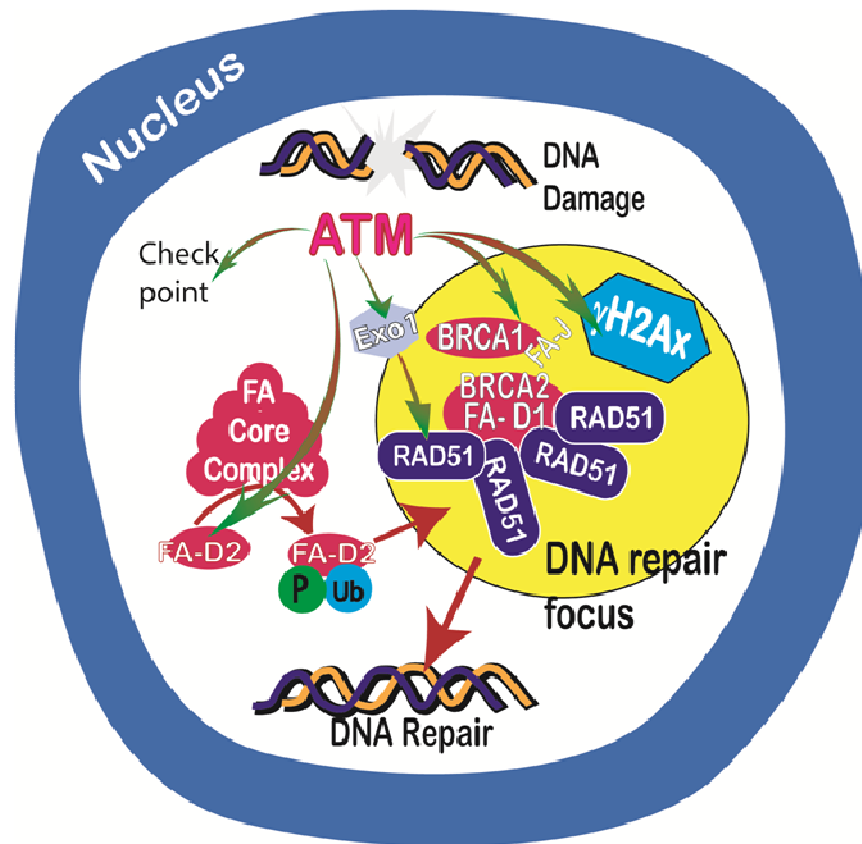


Figure 1. Working model for Summary DNA repair pathway containing BRCA1 and BRCA2 gene products based on D'Andrea and Grompe (2002); Venkitaraman (2003) and Bolderson et al (2010).

BRCA pathway components that have epidemiologic studies measuring risks for multiple cancers linked to known infections and inflammation are colored red. BRCA2 is the same as FA protein D1 and this is indicated. The red components are involved in repairing complex damage that occurs during inflammation. 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 FA-D2 which is then found in repair foci along with BRCA1 and BRCA2. 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). Inflammation also induces interstrand cross-links which characteristically require FA 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 the 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 related DNA damage, requiring several different types of repair (see text).

corresponding encoded proteins were essential to prevent cancers linked to chronic infection or inflammation. Risks for cancers associated with

inflammation in a specific organ were tested in known or likely mutation carriers.

From the database of 1250 articles, a shortlist was

identified, consisting of 24 cohort studies containing relative risk data for cancers other than breast and ovarian in mutation carriers. From the shortlist, 11 articles (some including several study arms) met inclusion criteria and passed exclusion tests (Figure 2). Table 1 summarizes details of included studies, associated infections with their cancer targets, and effect measures. Table 1 shows RR data from 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 determines in which organ the cancer occurs.

Homozygotes

For FA 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 and Table 2, top row), with onset accelerated into early ages. Liver cancers in FA homozygotes occurred at median age 13; cervical cancers in FA homozygotes had a mean age of 25; head and neck cancer occurred at mean age 28; and vulvar cancer had a mean age of 27.

Heterozygotes

Results in Table 2 for homozygotes and heterozygotes show that defects in genes required to prevent a chromosome breakage or instability syndrome increase risks for cancers associated with chronic inflammation. This is true for homozygous defects in a FA gene, and for inherited heterozygous deficits in the genes ATM, BRCA1 and BRCA2. Risks increase hundreds of times for homozygotes and up to several times for heterozygotes. Thus an infection known to cause chronic inflammation in a specific organ is more likely to lead to cancer in that organ if an inherited mutation is present.

RRs for stomach cancer in BRCA1 heterozygotes and cervical cancer in BRCA2 heterozygotes include 1 in the confidence intervals, perhaps because of a small number of events. To address these uncertainties, meta-analyses were performed by combining RR values for individual infection related cancers associated with mutation in any one of these genes. The calculations in the last row in Table 2 then represent 24,272 heterozygotes as 19,765 BRCA1/2 heterozygotes or potential heterozygotes and 4507 A-T heterozygotes or potential heterozygotes. These meta-analyses calculations make use of more data and do not require specific typing of BRCA1 vs. BRCA2 mutations. Combined values for any heterozygous gene mutation in the last row of Table 2 are similar to RR values obtained from individual included gene mutations in the rows

above. The confidence intervals for combined RR values for cervical and stomach cancer no longer include 1.

Data for head and neck cancer in heterozygotes is limited in Table 2 because the association with infection (HPV) is clearest for cancer of the oropharynx - the area of the head and neck posterior to the mouth (D'Souza et al., 2007). Oropharynx cancer was not measured as such in studies of known BRCA1/2 carriers (Table 1). Usually, cancers of the paranasal sinuses originate in the lining of the oropharynx or nasopharynx. Head and neck cancers as "buccal cavity and pharynx" in BRCA1 carriers gave a RR=0.15, but cancers of the paranasal sinuses were instead found among "other cancers" (Thompson et al., 2002). Paranasal sinus cancers may well have originated in the oropharynx (Tables 1 and 2). Because the head and neck region is anatomically complex, other structures overlap and are in close proximity to the oropharynx. BRCA2 heterozygotes have increased risks for head and neck cancers reported as cancers of the oral cavity and buccal cavity and pharynx (Table 2). A study of likely but untyped BRCA1/2 mutation carriers found high RR for oropharyngeal cancer (Evans et al., 2001).

Nonetheless, most testable risks for cancers linked to inflammatory conditions are exacerbated by the presence of a mutation in BRCA1, BRCA2 or ATM and this does not depend on whether statistical results from mutations in these different genes are combined. The working model used here places ATM, BRCA1 and BRCA2 gene products in the same pathway but results are also consistent with several models as alternatives to Figure 1 (Cohn and D'Andrea, 2008; Knipscheer et al., 2009; Whitby, 2010).

Limitations

Limitations of these results include comparatively small sample sizes because of the rarity of hereditary diseases. The RR values for heterozygotes (Tables 1 and 2) do not represent pure populations of heterozygotes. No study tested every member of a cohort for a mutation. Cohorts in some studies [e.g. Hemminki et al. (2005)] were not typed but were eligible for mutation testing based on personal or strong family histories (Syrja et al., 2004). Of course unique interactions and other critical cancer preventing functions of the individual gene products that are outside or peripheral to model pathways can cause errors. This is mitigated somewhat because the cancers in Table 2 are all mediated by chronic inflammation, so preventing them requires preventing complex DNA damage from chronic inflammation. Risks for cancers late in life are much more susceptible to competing risks and dropouts due to death from other cancers. Competing risks probably affect statistics for stomach cancer and make it especially difficult to measure risks

Table 1 Summary of data sources providing relative risk values for known infection related cancers in BRCA pathway mutation carriers

Gene variant Reference	Number of study participants	Infection and cancer target	Effect measure [95% CI]
FA homozygotes. Alter (2003)	1289 FA patients	HBV or HCV liver	RR = 574.1 [233.0 – 1414]
	356 female FA patients	HPV cervix	RR=76.61 [23.04-253.1]
	799 FA patients	HPV head and neck	RR=162.7 [91.83 - 287.7]
	356 female FA patients	HPV vulva	RR=1124 [550.3 – 2279]
FA homozygotes. Kutler et al (2003a, 2003b)	754 N. Amer. FA patients	HBV or HCV liver	RR =477.5 [184.2 – 1236]
	228 female FA patients	HPV cervix	RR=239.2 [92.16 - 615.6]
	228 female FA patients	HPV HNSCC (or EBV nasopharynx)	RR=203.4 [110.1 -374.3]
	228 female FA patients	HPV vulva	RR=1404 [649.0 -3001]
FA homozygotes. Rosenberg et al (2003)	145 FA patients:	HBV or HCV liver	RR =275.9 [61.89 – 1215]
	69 female FA patients	HPV cervix	RR=422.8 [105.9 -1597]
	145 FA patients:	HPV head neck (or EBV nasopharynx)	RR=333.3 [139.2 -776.2]
	69 female FA patients	HPV vulva	RR=2791 [906.7- 8033]
BRCA1 heterozygotes. Thompson et al (2002)	11,847 members of 699 families. 18.9% (2245) BRCA1 mutation carriers, 9.3% (1106) non-carriers, 71.7% (8496) untested.	HBV or HCV liver	RR=4.06 [1.77 -9.34]
		HPV cervix	RR=3.84 [2.33 - 6.33] women < age 65
		HPV (or EBV) HNSCC as Buccal cavity, pharynx.	RR= 0.15 [0.06 to 0.40] RR “other” cancers = 7.40 [5.14, 10.66] including paranasal sinus cancer (see text)
BRCA2 heterozygotes. Breast Cancer Linkage Consortium (1999)	3728 individuals including 50 men. 471 carriers; 390 non-carriers; 2186 untested. 596 female breast cancer patients diagnosed under age 60.	h.pylori stomach	RR=1.56 [0.91 - 2.68]
		HBV or HCV liver	RR=4.18 [1.56 -11.23]
		HPV cervix	RR= 1.29 [0.48 - 3.43]
		HPV HNSCC as buccal cavity & pharynx	RR=2.26 [1.09 - 4.58] p=0.06
ATM heterozygotes. Swift et al (1976)	27 A-T families from North America and Europe including 1639 individuals	h. pylori stomach	RR=2.59 [1.46 -4.61]
		HBV or HCV Liver, + bile duct + gallbladder (1 category until 1965)	SMR=5.00 [0.88 - 28.31] SMR=7.63 [1.24-46.9] for 1 primary liver cancer at age 36
		HPV cervix	RR= 3.03 [1.54 - 5.95]
BRCA1/2 heterozygotes. Evans et al (2001)	2785 women from Thames cancer registry: primary cancer following 2 breast-, 2 ovarian- or 1 breast- 1 ovarian- cancer.	h.pylori stomach	SMR=2.00 [0.72 -5.58]
		HBV or HCV liver	RR=1.84 [.05 -10.3]
		HPV oropharynx	RR=14.7 [1.73 -51.6]
		h. pylori stomach	RR=1.53 [0.62 -3.16]

Table 1 cont.

BRCA2 heterozygotes. Hemminki et al. (2005)	677 men diagnosed with breast cancer at age<56 pooled from 13 cancer registries with 60 men having a second cancer different than breast cancer.	HPV (or EBV) oral cavity pharynx	RR=1.94 [0.4 -5.66]
		h. pylori stomach	RR=3.82 [1.54 -7.87]
BRCA2 heterozygotes. Johannsson et al (1999)	383 male relatives and 345 females. 87 tumors among 728 relatives.	HPV cervix	SMR=4.21 [1.15-10.79]
		HPV (or EBV) oral cavity (head neck)	SMR=4.17 [0.11 -23.26]
		h.pylori stomach	SMR=1.63 [0.34-4.75]
ATM heterozygotes. Olsen et al (2005)	1445 blood relatives of 75 patients with verified A-T in 66 Nordic families. 712 women and 733 men.	HBV or HCV liver	RR=2.7 [1.37-5.44]
		HPV cervix	RR=3.1 [1.42- 6.82]
		h.pylori stomach	RR = 4.62 [2.86-7.51]
ATM heterozygotes. Geoffrey-Perez et al (2001)	1423 relatives of A-T patients from 34 families. 715 males and 708 females	HBV or HCV liver	Obligate RR=4.55 [0.06 - 25.3]; 50% carrier RR=7.69 [1.55 - 22.5] 25% carrier RR=7.69 [0.86 - 27.8]
		h.pylori stomach	Obligate RR=1.61 [0.02 -8.97]; 50% carrier 2.22 [0.45-6.49] 25% carrier 0.35 [0.001 - 4.31]

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. These cohorts were: patients diagnosed with FA in specialized clinics; all cases of FA from the literature; families having members with positive BRCA1 or BRCA2 test results based in large part on breast cancers in women younger than age 60; women from cancer registries with positive test results or high probabilities of being a BRCA1 or BRCA2 mutation carrier because of strong personal or family histories of breast and ovarian cancers at young ages; male breast cancer patients younger than age 60; cancers at age <60 in blood relatives of A-T patients. Homozygous FA is especially rare so cancer risk data originates from three studies involving about 2200 patients. These studies were conducted before some FA proteins were known. It was therefore necessary to consider FA proteins as a group. This is justified biologically because the proteins are all interdependent, function in a common pathway, and the phenotypes of different FA complementation groups are similar. In various studies of FA families, more than 60% up to 94% of mutations found were FA-A suggesting that FA-A mutations may dominate some cancer risk data (Bouchlaka et al., 2003). Homozygous FA patients develop cancers at very early ages when cancers in control populations are very rare. Control incidences needed to calculate RR for cancers in homozygous FA patients were from DevCan using the mean or median ages at which cancers found in FA patients occur in control populations Alter (2003), Kutler et al (2003). Survival was about 62% for cancers other than liver and this correction was made (Alter, 2003; Kutler et al., 2003). No survival correction was applied to liver cancer since it occurred at an average age of 13. Studies containing large numbers of cancers first diagnosed at age 60 or younger lessen somewhat the influence of sporadic cancers on effect measures. Coincidentally, risk factors in normal populations for viral infections associated with specific cancers are also higher at younger ages. Age 47 was used as the peak age for cervical cancer in normal women. **Inclusion and exclusion criteria:** 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. The reasons for this were as follows. Studies with the largest populations generally reported cancers at the most anatomic sites. Most studies of heterozygotes reported an elevated overall cancer risk especially at early ages, often with some unidentified sites. However every study showed increased risks for multiple identified cancers, with some cancers again occurring at relatively early ages. For serial studies representing the same population, only the largest study was used (3 studies excluded). Unpublished reports, single case reports and bone marrow transplant recipients were excluded. The same standard protocol was followed to extract data from each included study. Data were extracted several times performed weeks apart without referring to the previous trial. In some cases it was necessary to use cumulative control cancer incidences calculated using the NCI DevCan and SEER programs. NCI values were verified by comparison with published control values from numerous included references and always agreed well, showing that these control statistics were valid in these populations. All statistical results were further tested against independent evidence and theory. Statistical analyses were performed with StatsDirect software (StatsDirect, Ltd 2008) and checked with RevMan software.

Table 2. Cancer risks linked to chronic inflammatory infections at specific organ targets in cohorts with homozygous or heterozygous mutations in the pathway containing BRCA1 and BRCA2 gene products

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. (2003a), 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)

Results are summarized from data in Table 1 or calculations based on data in Table 1. Data for cancers of the liver, cervix, stomach and head and neck area are calculated 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 and ATM heterozygotes. For meta-analyses, the random effects model was used since it allows measured effects to vary across studies and estimates the inter-study effect variance with a simple non-iterative method (Dersimonian and Laird, 1986). Studies in meta-analyses were weighted according to this model. Random and fixed effects calculations almost always gave identical or very similar results. All reported p values were derived from two-sided statistical tests. Heterogeneity testing evaluated whether the effect size in different subgroups (defined biologically or medically) varied significantly from the main effect. The inconsistency of results across studies is summarized in the I^2 statistic, the percentage of variation across studies due to heterogeneity rather than chance. An I^2 value >50% generally indicates significant heterogeneity (Higgins et al., 2003). Heterogeneity was also calculated as non-combinability, and by a moment based method. Heterogeneity estimates can have large uncertainty, especially for few trials and were interpreted cautiously.

for a cancer such as colorectal cancer, which is rapidly lethal but occurs late in life.

Independent evidence agrees with the results in Table 2

Search results (Figure 2) also retrieved further independent evidence supporting the ideas that chronic

inflammation exacerbates cancer risks in mutation carriers and that it is likely to be important in determining where cancer occurs. The first type of evidence provides general support to relate pathway deficits and chronic infection and inflammation. Lymphocyte infiltration is present in all five organ specific cancers as a sign of chronic inflammation. FA and ATM homozygotes have

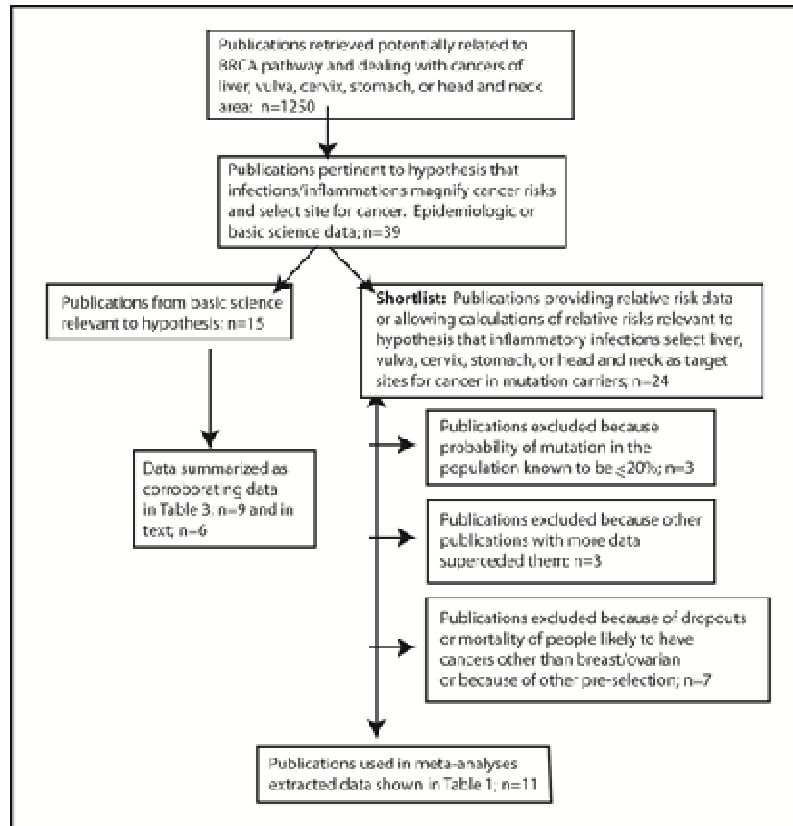


Figure 2. Flow chart showing search results for cancers with known links to chronic inflammatory infections in mutation carriers.

Initial searches were for RR data for cancers of the liver, cervix, vulva, stomach or head and neck area in carriers of mutations. Publications providing corroborating data contained any other relevant information from basic or clinical sciences. The numbers of publications in each category are indicated by values of n.

strong risk factors for viral hepatitis because they require multiple transfusions. Increased HCV seropositivity in Ashkenazi Jews suggests that ethnic factors might 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). HCV infection triggers mitochondrial changes releasing reactive oxygen and nitrogen species causing double strand breaks and DNA damage, but mock infected or uninfected control cells did not show detectable double strand breaks (Machida et al., 2006). Liver cancer does not develop unless chronic inflammation follows infection, leading to DNA breaks and other damage (Machida et al., 2006; De Marzo et al., 2007). Fa-c deficiency in mice exacerbates the inflammatory response (Sejas et al., 2007).

A second type of supporting evidence comes from mechanistic studies of DNA repair functions mediated by BRCA1 and BRCA2. Inflammatory cells in general produce reactive oxygen and nitrogen species which damage DNA. Responses requiring the gene products in

Fig 1 can be induced by reactive oxygen or nitrogen products from inflammatory processes which cause a wide variety of DNA damage (Nakano et al., 2009; Saito et al., 2003; Hadjur et al., 2001). This damage includes alkylation, deamination, oxidation and nitration of nucleobases, and single- and double-strand breaks, leading to increased levels of mutation (Sawa and Ohshima, 2005). BRCA1/2 and FA dependent homologous recombination is initiated by fork breakage at adducts produced by peroxy nitrite derived from macrophages. Peroxy nitrite oxidizes guanine in DNA producing an O-acyl-isourea structure that then reacts with proteins such as histones or glycosylases to form DNA protein adducts. 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 would thus favor dangerous gene rearrangements if less specific repair methods then operate (Friedenson, 2007). There are also many opportunities for interstrand cross-links,

Table 3. Independent evidence for increased risk in mutation carriers for cancer related to tissue specific chronic infections/inflammation

Interpretation	Supporting evidence	Reference
FA patients are highly susceptible to HPV mediated viral cancers.	54% of FA patients who develop cancers caused by HPV (e.g. cervical 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 (2003)
Defects in the pathway containing BRCA1 and BRCA2 are associated with human cervical cancer or other HPV linked diseases.	A mutated BRCA1 gene was detected in 13/17 biopsies of precancerous lesions of the cervix 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. 42% (34 of 81) of cervical cancers had an allelic imbalance at 11q23.1 (near or including the ATM gene) High risk HPV oncoproteins expressed in FA cells accelerate chromosome instability.	Park et al. (1999), Kadaja et al (2009) Skomedal et al. (1999).
Reduced activities of BRCA pathway components are associated with HCV infection and liver cancer.	Reduced activities of BRCA2, FA-J and ATM have been reported in HCV mediated human hepatocellular carcinoma in comparison to normal uninfected cells.	Ghaziani et al. (2006), Kondoh et al. (2001), Lai et al (2008),
BRCA2 mutation is associated with stomach cancer causally linked to chronic h.pylori infection	The standardized incidence ratio for stomach cancer in 29 BRCA2 families was nearly 600 times normal. Stomach cancer in Polish patients in other studies were also associated with BRCA2 mutations	Jakubowska et al. (2002), Jakubowska et al. (2003), Figer et al (2001).
3 pathogens strongly associated with cancer produce DNA damage. Some of this damage requires BRCA1/2, FA proteins or ATM for repair	HCV infection triggers mitochondrial changes releasing reactive oxygen and nitrogen species. This causes DNA double strand breaks. HPV-16 infection reduces reactive oxygen scavenging activity and makes cells unresponsive to H ₂ O ₂ damage. h. pylori infection inhibits reactive oxygen intermediate scavenging enzymes that prevent damage to gastric epithelial cells.	Machida et al.(2006). Lembo et al. (2006). Smoot et al. (2000)
Other cancers with probable links to inflammation strongly correlate with biallelic BRCA2 mutation.	Acute myeloid leukemias of the monocytic lineage can be induced reproducibly and with high incidence by collaborative effects of severe chronic inflammation and specific retroviral infections. In patients with mutation of both BRCA2 alleles, there are dramatic risks for specific cancers with strong associations to inflammation. Cumulative probability of leukemia (primarily AML) was 79% by age 10 years; of a brain tumor (primarily medulloblastoma) was 85% by age 9 years, of a Wilms tumor was 63% by age 6.7 years.	Wolff et al. (1991). Alter et al. (2007)

generally acknowledged to require FA proteins for correction. Another direct correlation is that the BRCA1 associated helicase FA-J is required to sense oxidative base damage in either strand of duplex DNA and unwinds the damaged DNA substrate in a strand specific manner (Suhasini et al., 2009).

Table 3 summarizes a third type of supporting evidence. Studies cited in Table 3 independently relate pathway mutations in FA, BRCA1/2 or ATM genes to increased risks for cancers associated with tissue specific chronic infection and inflammation.

Finally, many investigators have found 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. Inflammation is also

associated with prostate cancer. Exposure to infectious agents and dietary carcinogens, and hormonal imbalances leads to prostate injury, to chronic inflammation and to high risk lesions (De Marzo et al., 2007).

Potential associations of breast and ovarian cancer to infection and inflammation are much more difficult to evaluate

In contrast to the evidence linking cancers in mutation carriers to known infections, there are no known infections definitively linked to breast or ovarian cancer. It is still possible that breast and ovary are targeted for hereditary cancers because of inflammatory processes which have not yet been well characterized. Table 4 summarizes evidence from nearly 30 studies that inflammation participates in targeting ovary and breast in mutation carriers.

Hereditary ovarian cancer and infection/inflammation

Regardless of mutation status, much ovarian cancer begins in the fimbriae - fingerlike projections terminating the fallopian tubes where the ovum released from the ovary is collected. The distal fallopian tube has emerged as an important locale for early serous and endometrioid carcinomas in BRCA+ women as well as women undergoing surgery for ovarian cancers (Table 4). Very high percentages of primary cancers are found in the fallopian tubes, up to 5 per 100 women undergoing prophylactic surgery (Hirst et al., 2009; Semmel et al., 2009). Seven consecutive ovarian cancers in mutation carriers were all in the fallopian tube (Table 4). Fimbrial cancers are difficult to distinguish from ovarian cancer because of large areas of intimate contact between fimbria and ovary. The fallopian tube cancer designation requires a dominant mass and evidence of an early cancer there. However ovarian tumor bulk may be greater. In the past, ovarian and tubal cancers were grouped and coded together (Thompson et al., 2002).

Four epidemiologic studies all show that tubal ligation protects mutation carriers against ovarian cancer and at least 30 publications show this for non-mutation carriers (Table 4). Tubal ligation commonly removes sections of tubes between the uterus and fimbria, presumably preventing infection/inflammation from reaching the fimbriae/ovaries. Ovulation itself may also contribute to inflammation by causing oxidative injury to 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). Use of oral contraceptives reduced RR for ovarian cancer by 7% for each year of use (Siskind et al., 2000).

Table 4 also summarizes other associations between infection / inflammation and fimbrial-ovarian cancer. These include evidence of inflammation in fallopian tubes and in ovaries removed during prophylactic surgeries. Ovarian cancer may also be associated with use of perineal talc, which promotes inflammation (Gates et al., 2008).

Many studies find that anti-inflammatory NSAIDs reduce ovarian cancer risk in nulliparous women although results sometimes conflict. Covariates may be responsible for this inconsistency. After adjustment for covariates, NSAIDs were inversely associated with ovarian cancer in women who never used oral contraceptives (OR = 0.58, 0.42–0.80). NSAID use was also associated with reduced risk in nulliparous women (OR = 0.47, 95% CI 0.27–0.82) (Wernli et al., 2006). The presence of intra-epithelial CD8+ T-cells (cytolytic or “killer” T cells) significantly correlates with loss of BRCA1

(Clarke et al., 2009; Fleming et al., 2006). CD8+ T cells are generally classified as having a pre-defined cytotoxic role within the immune system and are capable of inducing the death of cells that are infected with viruses (or other pathogens), or are otherwise damaged or dysfunctional. This association further links inflammatory cells and BRCA1 deficits. If the condition is not resolved, then CD8+ cells become an immune response that favors further genomic instability in the tumor. For serous ovarian carcinomas, the presence of intra-epithelial CD8+ T-cells correlated with improved disease-specific survival but not with progression free survival or overall survival (Clarke et al., 2009).

Prophylactic removal of ovaries increases risks for primary peritoneal cancer (Table 4), which occurs in up to 5% of patients. One explanation is that wound healing increases risks for cancer in surrounding tissues. Inflammation is an essential process that occurs early in wound healing.

Hereditary breast cancer and infection / inflammation

The origins of breast cancer in mutation carriers are not well understood. Table 4 summarizes evidence that inflammation may also participate in selecting the breast for cancer. T-cell lobulitis was frequently found in morphologically normal breast lobules removed during prophylactic mastectomies (Hermsen et al., 2005). The failure to find any premalignant or malignant lesion in the presence of lobulitis suggests that there is an immune response before the onset of hereditary breast cancer.

BRCA1 associated breast cancers have more and denser lymphocytic infiltration than sporadic cancers in a matched control group (Adem et al., 2003) and Table 4. Some extracted infiltrating lymphocyte populations may have tumor killing activity in vitro, suggesting the tumor overcomes such protective functions. A T-lymphocytic infiltrate is also closely associated with medullary breast carcinoma (Table 4), a rare cancer that is more frequent in BRCA1/2 mutation carriers. The medullary cancer infiltrate contains CD4+ (helper) and CD8+ T-cells but few tumor killing NK cells. Kuroda et al. (2005). There is a strong signature for an interferon induced pathway in some breast cancer, ovarian cancer and childhood leukemia. This infection associated gene signature suggests a deregulated immune or inflammatory response to some pathogen (Table 4). In BRCA1/2 carriers, lymphoid cells are themselves at high risk for becoming malignant (Friedenson, 2007). Hematopoietic malignancies would make immune responses in mutation carriers less effective in clearing infection and removing abnormal cells.

Table 4. Inflammation is an important factor in determining the organ that develops cancer in mutation carriers.

Conclusion	Evidence of association with inflammation and BRCA1/2 mutation carriers or potential carriers.	Evidence in women with no known mutation in the pathway containing BRCA1/2
Much ovarian cancer begins in fallopian tubes where inflammation occurs	Contralateral tubes from 14 fallopian tube cancers were twice as likely to have evidence of chronic inflammation (p=.0089), suggesting bilateral tubal disease preceding the cancers. Demopoulos et al. (2001).40-100% of "ovarian cancers" were actually fallopian tube cancers Crum et al. (2007). 7 consecutive cancers in BRCA+ women all originated in the fimbrial or ampullary region of the tube. Callahan et al (2007). There was no exclusively proximal disease. Cass et al. (2005)	A rough estimate is that tubal cancer is involved in 15% of ovarian cancers (Crum et al. ,2007). Risk for fimbrial cancer in normal women is not known.
Tubal ligation prevents ovarian cancer in mutation carriers and in normal women. Fallopian tube cancer originates in distal tube suggesting infection/ inflammation travels through the tube.	In mutation carriers, pooled OR = 0.69 (95% CI = 0.55-0.85). For BRCA1 carriers, HR=0.49 (0.22-0.80) McGuire et al. (2004), McGlaughlin et al. (2007), Narod et al. (2001), Rutter et al. (2003), Antoniou et al (2009). OR based on a total of 3070 BRCA1 and BRCA2 carriers. HR from 2,281 BRCA1 and 1,038 BRCA2 carriers. Antoniou et al (2009)	30 publications show an inverse association with ovarian cancer risk based on data from hundreds of thousands of women.
Oral contraceptives protect against ovarian cancer consistent with preventing inflammatory processes by suppressing ovulation	HR = 0.52 [0.37-0.73] for BRCA1 carriers who used OC. Increasing duration of OC use was associated with a reduced ovarian cancer risk. Data from 2,281 BRCA1 and 1,038 BRCA2 carriers. Antoniou et al (2009).	Oral contraceptives reduced RR for ovarian cancer by 7% for each year of use. Siskind et al. (2000)
Intraepithelial tumor infiltrating lymphocytes, macrophages as evidence of inflammation are found in ovarian cancers	17/ 18 cases with BRCA1 mutation or epigenetic silencing of BRCA1 expression had intraepithelial CD8+ tumor-infiltrating lymphocytes Clarke et al. (2009).	11 of 19 sporadic cases had tumor infiltrating lymphocytes Clarke et al. (2009) Macrophages may also be found in ovarian tumors. Fleming et al. (2006)
Anti inflammatory drugs reduce risks for ovarian cancers	Well known anti-inflammatory agents Not separately studied in mutation carriers	487 ovarian cancer cases and 2653 controls. Nulliparous OR=0.47(0.27-0.82) Never users of oral contraceptives OR=0.58 (0.42-0.80) Wernli et al. (2008).
Prophylactic surgery and oophorectomy in women with a strong family history of ovarian cancer increases cancer risks in surrounding tissues. These cancers may be associated with inflammation during wound healing.	6/324 women who underwent prophylactic removal of ovaries developed primary peritoneal carcinoma Piver et al. (1993). Also 13 peritoneal cancers as the most frequent site of "other" cancers in Thompson et al. (2002) with 2245 known carriers.	
Talc in the perineal region causes inflammation and reaches the ovaries where it predisposes to ovarian cancers		RR as high as 4.8 (2.1-11). Gates et al. (2008).
Breast inflammation as lobulitis occurs in mutation carriers before there is evidence of breast cancer	21/41 prophylactic mastectomy specimens in high risk women had inflammatory lobulitis before onset of cancer. Hermsen et al (2005).	8/82 controls (p < 0.0001) Hermsen et al (2005).
Breast cancers in BRCA1/2 mutation carriers are more likely to have an inflammatory response or a denser inflammatory response	BRCA1/2 mutation carriers have a denser lymphoid infiltrate in breast cancers vs a matched, sporadic cancer control group. Adem et al (2003). BRCA1 related cancers had higher mitotic counts and more lymphocytic infiltration than sporadic, control) cancers Lakhani et al (1998), OR=1.90 (1.31-2.76) mild and 2.46(1.26-4.79) prominent, 114 subjects with mutations in the BRCA1 gene. 1046 observations from 528 control subjects with cancers unselected for family history Lakhani et al (1998). Medullary cancer is more frequent in BRCA1/2 mutation carriers and 13/13 cases had a dense T-lymphocyte infiltrate, with few NK cells. Kuroda et al. (2005). Microarray data shows 16/18 BRCA1 positive tumors have higher lymphocyte infiltrate based on higher expression of lymphocyte specific genes van't Veer et al (2002).	3/52 cancers from women with no mutation detected had lymphoid infiltrates vs. 23/157 in matched sporadic controls Adem et al (2003). Medullary breast cancer is rare in normal women

Table 4 cont.

Increases in inflammatory responses accompany transition steps leading toward breast cancer		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 (Hussein and Hassan, 2006).
Genes important for immunity to viral infection / inflammation are essential to prevent breast cancer but are abnormally expressed in BRCA1 carriers	BRCA1 expression is essential to up regulate a group of IFN- γ regulated genes including an anti-viral protein (8-fold) and an antigen presentation protein (2-fold) Buckley et al (2007). Einav et al (2005)	40% of 96 breast cancer samples had a strong signature for an interferon induced pathway Einav et al. (2005).
Abnormal retroviral protein expression may contribute to hereditary and sporadic breast cancer.	Strong evidence of ongoing immune response in breast cancer patients including antibody, T-cell responses against HERV antigens and interferon- γ induction 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). High titer retroviral RNA was expressed in circulating blood from 20 breast cancer patients Contreras-Galindo et al (2008). Most breast cancers occurred in younger age patients . but BRCA status was not determined. Wang-Johanning et al. (2008).	8 to 25 normal controls Wang-Johanning et al. (2008).
Anti-inflammatory drugs reduce risks for breast cancer	3546 women with a family history of breast cancer followed for 1 -<=5 years. RR 1-4 years of follow up was 0.6 [0.38-0.92] and at >=5 yrs RR=0.62[0.41-0.93] The biggest preventive effect on breast cancer risk was for women with a family history of breast cancer. Harris et al (2003)	RR=0.88 (0.84-0.93) meta-analysis of 38 studies Takkouche et al. (2008) 5 meta-analyses involving millions of subjects and up to 91 studies find that NSAIDs protect against breast cancer.

There are no known chronic inflammatory infections definitively linked to breast or ovarian cancer. Studies summarized in the table show cancer prevention data and evidence of immune responses before the onset of cancer. These studies support the idea that inflammation is an important factor in determining the organ that develops cancer in mutation carriers.

Viruses including EBV, a human equivalent of murine mammary tumor virus (MMTV), and HPV have been detected in benign breast tissues and breast tumors. All are potential candidates as sources of infection and inflammation that 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. However other investigators could not find evidence for HPV sequences in invasive carcinomas (De Cremoux et al., 2008).

Candidate sources for infection / inflammation underlying breast cancer also 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 (Table 4).

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 (Table 4). 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 strongest 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 missing, 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 was 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 (Table 4). However confidence intervals overlapped other strata (Harris et al. 2003).

DISCUSSION

This analysis establishes for the first time that carriers of mutations in a model pathway containing BRCA1 and BRCA2 are inordinately susceptible to organ specific cancers associated with chronic infections and inflammatory processes. The increases in cancer risks can be so large that inflammatory processes effectively determine the site for cancers associated with inherited deficits in BRCA1/2, ATM or FA genes.

Under some conditions, the immune response in normal individuals clears the source of the chronic inflammatory condition. If the source cannot be resolved, molecules that damage or break DNA, including superoxide, hydrogen peroxide, singlet oxygen, and nitrogen oxides are perpetually released from activated phagocytic inflammatory cells. In the host, lymphocytes and other cells are attracted to the site. Cells and host DNA in this environment are continually damaged and must be repaired or replaced, thereby increasing risks for dangerous mutations. Inherited deficits in repair processes such as those in Figure 1 then make mutation carriers inordinately more likely to develop cancer in the organ that contains the inflammatory process.

Not only do genetically related cancers typically occur at young ages but specific cancers associated with viral infections have peak occurrences in younger victims. Viral hepatitis and HPV infections have peak incidences in younger people where risk factors are typically greater and risky behavior is more frequent. The peak age for cervical cancer in women is age 47. Head and neck cancer associated with HPV infection in normal males occurs as cancer of the oropharynx and tonsils with peak ages 55-59 [NCI SEER data]. In contrast, many sporadic cancers that are not associated with known infections typically occur at older ages. A failed host response to viral infection might also increase the rates of viral mutation, thereby making infections more dangerous.

A current view is that constant tissue damage leads to extended activation and proliferation of specific stem cell reserves. This would occur in each of the organs described in this analysis. Hematopoietic stem cells are activated in response to chronic infection. Baldrige et al. (2010) provided evidence that long term replenishing hematopoietic stem cells can respond directly to IFN- γ stimulation in the context of a chronic infection. Inherited defects in repair requiring BRCA1/2 gene products then amplify risks from chronic inflammation and this may contribute to observed increases in risk for certain hematopoietic cancers (Friedenson, 2007). In ovarian cancer, a proinflammatory peptide promotes the engrafting of progenitor cells known as multipotent stromal cells or mesenchymal stem cells into the stroma where they potentiate tumor progression (Coffelt et al., 2009).

At first glance, the role of inflammation in targeting hereditary cancer to the breast does not appear to match

results that find differences in hereditary vs. sporadic cancers in histologic type, grade or receptor status. However, different cells / or stem cells can become malignant during a chronic inflammatory process, which typically involves multiple cell types and surrounding tissue. That this occurs for hereditary ovarian cancer or breast cancer is suggested by finding healed chronic inflammation in contralateral fallopian tubes, by the ability of tubal ligation to prevent ovarian cancer, by finding inflammation in the absence of cancer in prophylactic mastectomy specimens and by other evidence cited in Table 4.

Another explanation may involve structural differences. Breast tissue of women with a background of familial breast cancer shows breast fibrosis and less breast differentiation than control or normal tissues. So the architectural pattern is different from control or normal tissues (Russo et al., 2001; Russo et al., 2008). This suggests that BRCA-1 or related genes may have a functional role in the branching pattern of the breast during lobular development, and this affects the epithelial stroma interaction. Breast tissue from mutation carriers has lost the connective tissue that separates inflammatory cells of the immune system from intralobular structures (Russo et al., 2001). This removes a limit on the area exposed to inflammatory mediators and could increase risks from inflammation. Missing connective tissue would also favor spread of malignancy.

In a repair-deficient genetic background, chronic inflammation in a specific organ disproportionately increases cancer risks and becomes an important reason that a particular organ develops cancer. Inactivating ATM, BRCA1, BRCA2 or FA genes will interfere with repair of some kinds of damage caused by inflammation. However inflammation may not be the only reason a specific organ is targeted. The cancer targets here include hormone responsive organs in the female reproductive system and the liver where they are metabolized. Sex hormones are well known as modifiers of the inflammatory response.

Recently defined mechanisms can also contribute to explaining why breast and ovary are especially at risk in BRCA1/2 individuals. Deficiencies of BRCA1 or BARD1 and/or upregulation of BARD1 isoforms lead to estrogen receptor alpha upregulation, providing a functional link between BRCA1 deficiency, estrogen signaling and tumorigenesis (Dizin and Irminger-Finger, 2010). BARD1 can also induce the transcriptional activity of the inflammatory factor NF-KB (Irminger-Finger and Jefford, 2006). This represents another layer that defends the genome. 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). The pathway containing BRCA1/2 is probably essential to prevent some cancer related gene rearrangements

(Friedenson, 2007).

CONCLUSION

A new finding here is that inheriting a mutation that disables BRCA1, BRCA2, or related proteins inordinately increases cancer risks from infection and inflammation. These increases can be so large that the site of infection or inflammation effectively determines cancer tissue specificity. Controlling chronic infections and inflammation may be a helpful option to prevent or delay cancers in mutation carriers.

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