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Preventing hereditary cancers caused by opportunistic carcinogens

Bernard Friedenson, Ph.D.

Department of Biochemistry and Molecular Genetics
College of Medicine
900 S Ashland Ave
University of Illinois Chicago,
Chicago, IL 60607

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Cancer prevention in mutation carriers

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Objectives

Previous studies reported inherited BRCA1/2 deficits appear to cause cancer by impairing normal protective responses to some carcinogens. Opportunistic carcinogens can exploit these deficits by causing chronic inflammation, constant cell death and replacement in a mutagenic environment, DNA crosslinking or double strand breaks. Some of the resulting cancers may be prevented if BRCA1/2 specific carcinogens are identified.

Methods

The literature was systematically searched for carcinogens capable of exploiting deficits in BRCA1/2 pathways. Search criteria were common exposure, available information, required BRCA1/2 pathway repairs, increased risks for any cancer, and effects on stem cells.

Results

Formaldehyde and acetaldehyde are closely related carcinogens and common pollutants that are everywhere. Alcohol metabolism also produces acetaldehyde. High levels of either carcinogen overwhelm normal detoxification systems, cause inflammation, inhibit DNA repair and produce DNA cross links as critical carcinogenic lesions. Searching model system studies revealed both carcinogens activate stem cells, BRCA1/2 pathways and connected BRCA1/2 pathways to myeloid leukemia. For example, the BRCA1-BARD1 complex is required for proper nucleophosmin functions. Nucleophosmin prevents a major subset of acute myeloid leukemia (AML). Next, these concepts were independently tested against risks for myeloid leukemia. Epidemiologic results showed that BRCA2 gene defects inherited on both chromosomes increased risks so dramatically that AML occurs in most children. Using data from 14 studies, known/potential heterozygous BRCA1/BRCA2 mutations increased risks for myeloid leukemias by at least 3 fold in 7 studies and by at least 50% in 12.

Acetaldehyde occurs in breast milk. In model studies, excessive acetaldehyde/alcohol exposure affects estrogen metabolism and stimulates alternate alcohol detoxification pathways. These pathways can cause DNA cross linking by releasing oxygen species and activating procarcinogens. Acetaldehyde in rats' drinking water increased incidence of leukemias, lymphomas, pancreatic cancers and fibroadenomas. Human epidemiologic studies showed increased premenopausal breast cancer risks associated with persistent/high acetaldehyde levels related to alcohol metabolism genotype.

Conclusions

Although it is difficult to prove direct causation, BRCA1/2 mutation carriers may reduce cancer risks by avoiding excessive formaldehyde and acetaldehyde. Broader genetic testing and pharmacologic/nutritional detoxification are possible.

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Background

Previous explanations for the tissue specificity of hereditary breast cancer. BRCA1 and BRCA2 mutations were thought to have an exquisite specificity in causing breast and ovarian cancer. Published explanations either required some unique, tissue specific property of BRCA1/2 genes, depended on the context of other expressed genes, or on the absence of backup systems specific for tissues where tumors develop,

One idea is that cancer occurs in the breast because the breast does not have back up systems or redundancy to compensate for the absence of BrCA1/2 functions. Back ups for some BRCA1/2 function are general methods of DNA repair such as non-homologous end joining, or translesion synthesis. These systems have wide tissue distribution. When forced into service inappropriately because of abnormal BRCA1/2 pathways, repairs become less accurate and risks for some cancers increase. [e.g. Venkitaraman (2003), Lagerqvist (2007), Friedenson (2007)]. Cancers that depend on gene translocations may occur because double strand breaks are repaired by combining the wrong pieces of broken chromosomes. One cancer strongly associated with a reciprocal translocation is mantle cell lymphoma. The incidence of mantle cell lymphoma increased 70 fold when the pathway molecule ATM was inactivated [Friedenson, 2007]. At least in some cases, losses of whole chromosomes or fragments are so fundamental and essential that alternative mechanisms in different tissues are unable to compensate without increasing mutations. Repair or bypass of lesions using alternative methods has been documented, but this is known to increase the rates of mutation [Lagerqvist et al. (2008)].

A related proposal is that cells that lose both copies of BRCA1 are only able to survive in breast and ovary but die everywhere else. However there are homozygous defects if not in BRCA1, then in BRCA2, ATM and Fanconi proteins. In these conditions every organ survives.

Another proposal depends on the high proliferation rates in the breast and ovary. Cell proliferation in the absence of BRCA1 or BRCA2 may lead to a higher mutation rate. However breast cancer and leukemias provided foundations for the cancer stem cell hypotheses. This hypothesis states that cancers originate from stem cells that give rise to cancer, are capable of self renewal, differentiate asymmetrically but ordinarily do not proliferate. Past results show that continual proliferation in a mutagenic environment undoubtedly contributes [Friedenson 2010a,b].

Another possibility is that tissue specific cofactors, transcription factors, hormones and the context of different tissues determine the tissue specificity of hereditary cancers. However there are increased relative risks for cancers in a wide variety of tissues and increased risks for cancers in general.

Because of such problems with previous explanations for the tissue specificity of BRCA1/2 associated cancers, an alternate explanation for the tissue specificities of hereditary cancer was developed. Previous results suggested that hereditary cancers have defects in processing some carcinogens from the environment because hereditary defects aggravate the effects of

some carcinogens. Thus there was an increased incidence of cancers caused by organ specific infections that cause DNA damage requiring BRCA1/2 repairs. Other genes that encode for immune responses, for processing, detoxifying or metabolizing carcinogens are a first defense against these carcinogen induced cancers.

The literature was systematically searched to identify opportunistic carcinogens that act by exploiting deficits in BRCA1/2 pathways. Initial search criteria were common exposure, available information, required BRCA1/2 pathway repairs, increased risks for any cancer, and effects on stem cells. Conclusions were then tested against the ability of carcinogens to cause tissue specific cancers by exploiting known hereditary deficits along routes of exposure.

Methods

Links among mutations in BRCA1/2 pathways and common carcinogens. Searches were conducted for common carcinogens that produce DNA cross links or DNA protein cross links. Formaldehyde and acetaldehyde were identified as two common pollutants that form DNA lesions requiring BRCA1/2 pathway repairs. Both chemicals are carcinogens with known or suspected links to myeloid leukemia. Literature describing myeloid leukemia was searched for relationships to pathways mediated by BRCA1/2 gene products.

Risks for cancers associated with common environmental carcinogens in carriers of mutations in BRCA1/2 pathways. Cancer survivors are often followed prospectively for treatment response and complications, as well as disease progression. Given the high risk of BRCA1/2 mutation carriers and their involvement with medical oncology personnel, cancer survivors among patients with BRCA1/2 pathway mutations have often been monitored for the development of a second primary cancer. This is more often done than to observe genetically typed healthy individuals for the development of a first cancer. Thus studies of second primary cancers provided the most extensive and complete sources of data.

As previously described [Friedenson (2005, 2007, 2010a,b)], the literature was systematically searched for relative risk data on second primary cancers in carriers or likely carriers of mutations in genes encoding pathways that depend on BRCA1/2 genes. Data found in appropriate studies was used directly without further statistical calculation or combination. No exclusions were made for percentages of mutation carriers in the population, for survival, or for loss of subjects to follow-up.

Results

Formaldehyde and acetaldehyde were identified for this study because exposure is common; risks for several cancers increase; much information is available; there are connections with BRCA1/2 pathways, and both have effects on stem cells. [Zhang et al. (2010), Agency for toxic substances and disease registry (2010), Baan et al. (2009), US Dept Health and Human Services (1999), National Toxicology program (2011)].

Common and widespread exposure. Formaldehyde and acetaldehyde are chemically closely related. Both are common pollutants. Widespread human exposures to formaldehyde and acetaldehyde occur during manufacture and use of many maufactured products. Many millions of pounds of each chemical are produced each year [Agency for toxic substances and disease registry (2010), Baan et al. (2009), Hauptmann et al. (2009), National Toxicology Program (2010), Andersen et al. (2010), Friedenson, 2011].

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These carcinogens are also present in some foods and acetaldehyde is a metabolite of alcohol metabolism.

Formaldehyde and acetaldehyde are opportunistic carcinogens causing DNA damage that requires repairs by BRCA1/2 pathways.

Formaldehyde and acetaldehyde chemically cross-link strands of DNA to each other and to nearby proteins (Fig. 1). These lesions are probably critical for formaldehyde carcinogenesis [Zhang et al (2010)] and have been demonstrated by a large number of studies in vitro, in exposed animals and in circulating lymphocytes of exposed people [Zhang et al. (2010)] Acetaldehyde also causes DNA protein cross links (Figure 2).

Carriers of mutations in BRCA1 or BRCA2 genes are deficient in the ability to repair cross-linked DNA. Homologous recombination involving pathways containing BRCA1/2 has been demonstrated as essential to correct DNA protein cross links [Yamazoe et al. (2004), Nojima et al. (2005)]. Many studies in model systems support roles for BRCA-Fanconi pathways in repairing DNA protein cross links.

Formaldehyde can exist as polymers of varying length which may form cross linkers with varying reach. The reactions of formaldehyde in DNA-protein mixtures, have been studied using mixtures of deoxynucleosides and amino acids as model compounds Cross-linked products that were chemically irreversible, stable and readily isolated were formed with the amino acids cysteine, histidine and tryptophan. These products would form protein DNA cross links requiring BRCA1/2 pathway mediated repairs [Nakano et al (2003, 2007)]. Lysine cross-linked products were labile in solution, supporting widely reported reversibility of formaldehyde-induced cross-links between lysine rich histones and DNA [Lu et al. (2010)].

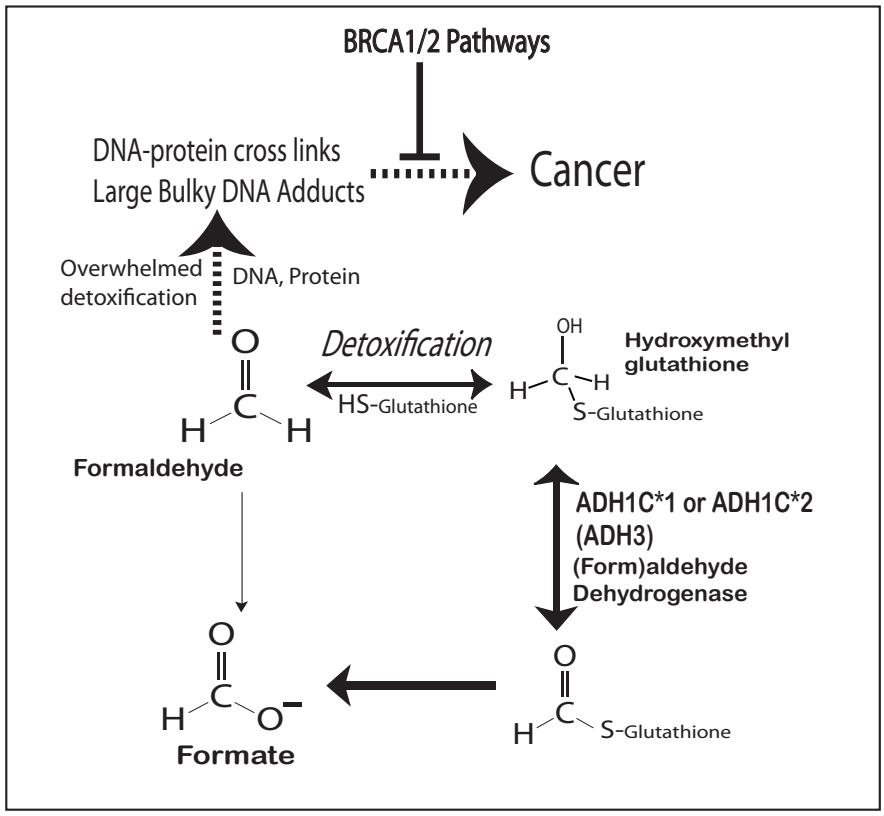

Figure 1 - Carcinogenesis at high levels of formaldehyde competes with formaldehyde detoxification mechanisms. Detoxification of low levels of formaldehyde occurs primarily by a pathway (thicker arrows) involving formaldehyde dehydrogenase (ADH1C*1 or ADH1C*2), an aldehyde dehydrogenase. The pathway converts formaldehyde to formate which is then eliminated in the urine, broken down to CO2 and water or enters the single carbon pool. Alternate, less used pathways are indicated by thinner arrows. Detoxification does not involve BRCA1/2 but BRCA1/2 pathways inhibit carcinogenesis.

In mice, the Brca pathway is among the top 10 most significantly enriched pathways after

1 week of exposure to 6 ppm formaldehyde [Andersen et al, 2010].

DNA-protein cross-links exhibit a dose-response relationship to formaldehyde exposure in the respiratory tract of laboratory animals at exposure concentrations relevant to human exposures. In peripheral white blood cells of occupationally exposed workers, DNA-protein cross-links increased significantly vs. controls and had a linear relationship with years of exposure [Shaham et al. (1996)].

BRCA1/2 related pathways also participate in preventing formaldehyde related collateral DNA damage e.g. bone marrow toxicity and immunosuppression (which can reactivate latent viral infections), and inflammation (which can produce cross-links due to oxidative damage). This collateral damage generates a mutagenic environment and increases the probability that AML stem cells will arise.

Alcohol consumption is causally related to an increased risk of cancer of the upper aerodigestive tract, liver, colorectum, and female breast. Several lines of evidence indicate that acetaldehyde, the first product of alcohol metabolism, plays a very important role in alcohol-related carcinogenesis. Excess acetaldehyde generated from alcohol metabolism can also produce DNA lesions that form interstrand crosslinks (Fig 2) Acetaldehyde exposure results in a concentration-dependent increase in Fanconi D2 monoubiquitination, which is dependent upon the proper functioning of the pathway. Acetaldehyde also stimulates BRCA1 phosphory-

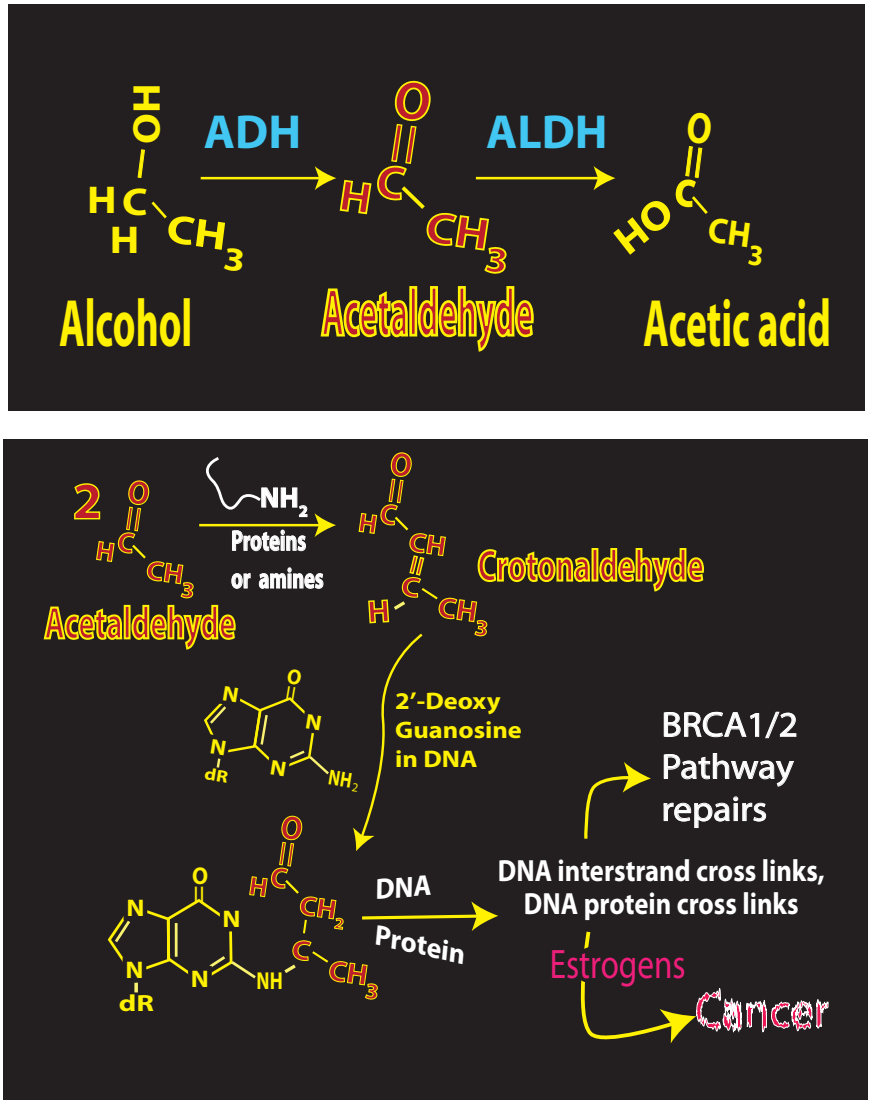

Figure 2a. Normal detoxification of alcohol requires two enzymes, alcohol dehydrogenase (ADH) and then aldehyde dehydrogenase (ALDH). Alcohol dehydrogease produces acetaldehyde, a mutagen and carcinogen. Genotypes for both enzymes influence the susceptibility to alcohol related carcinogenesis. Fig 2b. One mechanism or carcinogenesis. Acetaldehyde that escapes detoxification pathways can form crotonaldehyde, a reaction catalyzed by amine groups from proteins or naturally occurring amines. Crotonaldehyde is genotoxic, mutagenic and carcinogenic and can be derived from beer, wine and liquor. Reactions with deoxyguanosine in DNA produce DNA interstrand cross links and DNA protein cross links [Theravathu et al (2005)]. Some of these lesions require repairs by BRCA1/2 pathways. Inherited mutations within these pathways disable cross link repairs and can lead to cancer in exposed organs. Excessive alcohol/acetaldehyde can also affect estrogen adding to cancer risks.

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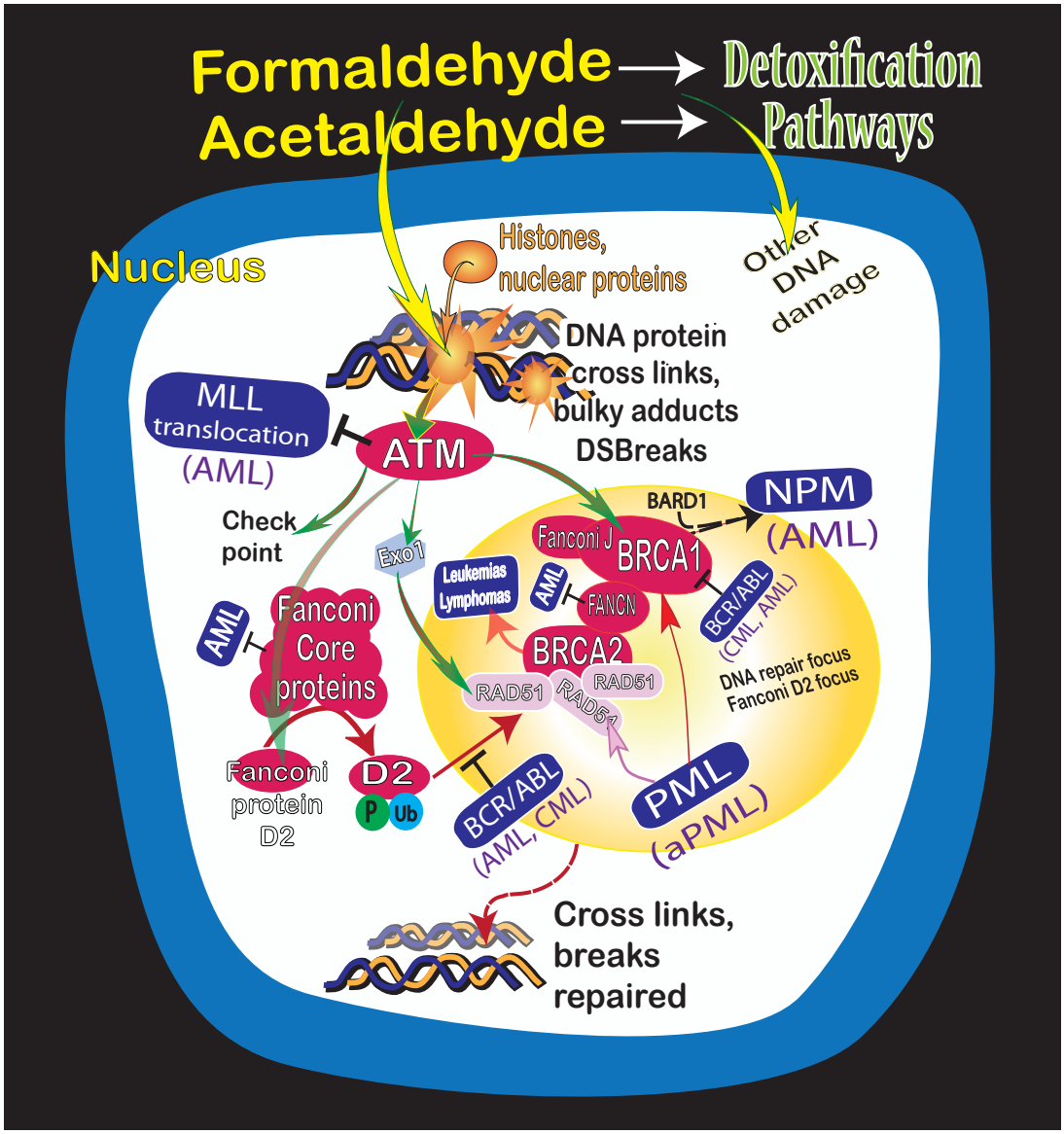

Figure 3 - BRCA1 and BRCA2 in DNA damage repair pathways showing probable links to myeloid leukemia, other leukemias and lymphomas. BRCA1 and BRCA2 are shown in pathways to correct DNA cross links and double strand breaks caused by formaldehyde, acetaldehyde and other agents that cause bulky addition products or DNA cross-links. DNA damage is more likely if the carcinogen escapes metabolic detoxification pathways (Fig. 1). Hereditary inactivation of a Fanconi gene causes Fanconi anemia, inactivation of the ATM gene causes ataxia-telangiectasia (A-T), and inactivation of BRCA1 or BRCA2 associates with hereditary breast/ovarian cancers. Proteins encoded by genes related to these well known hereditary cancer conditions are colored red. The dark boxes in the figure indicate proven links to myeloid leukemia. The BRCA1-BARD1 complex is required to activate the NPM gene which is lost in a subset of AML. In AML and CML, the BCR/ABL protein interferes with the formation of nuclear Fanconi protein D2 repair foci. In CML, BRCA1 becomes almost undetectable. The PML protein is required for Rad51 repair focus formation providing another link to leukemia. Family history of leukemia increases risk for breast cancer. Chromosome 13q is deleted in a subgroup of leukemias and lymphomas. Multiple other pathways also participate in repairing DNA damage but the pathway shown has been implcated in coordinating repairs..

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lation in a dose-dependent manner. Thus the pathways required to repair DNA damage from acetaldehye is qualitatively similar to pathways required to repair damage from mitomycin C. Mitomycin C is a known DNA crosslinking agent that has become a functional test for activity of pathways involving Fanconi proteins [Marietta et al (2009)].

Detoxification by specialized metabolic pathways. Normal metabolism produces both aldehydes and they occur naturally in foods. These background sources are generally too low to cause permanent harm and are managed by reactions and metabolism within the digestive tract. Formaldehyde is primarily metabolized by glutathione-dependent formaldehyde dehydrogenase (ADH3, existing in two forms renamed as ADH1C*1 or ADH1C*2) and aldehyde dehydrogenases (ALDHs) enzymes in alternative pathways (Fig. 1). Formaldehyde is converted to formate, which is then eliminated in the urine as a sodium salt, broken down to CO_2 and water, or entered into the single-carbon pool [Teng et al. (2001, Andersen et al, (2010)]. Other alcohol and aldehyde dehydrogenases can also contribute. Alcohol metabolism generates acetaldehyde and utilizes ADH and ALDH enzymes (Fig 2).

DNA cross-links, chromosome breaks and chromosome abnormalities are favored if environmental formaldehyde or acetaldehyde exceeds the capacity of metabolizing detoxification pathways (Figs 1 and 2). For formaldehyde, exogenous addition products form with DNA in a highly nonlinear fashion; a 21.7-fold increase in exposure of rats to labeled formaldehyde caused a 286-fold increase in DNA-formaldehyde addition products [Lu et al. (2011)]. For both aldehydes different variants of the genes encoding detoxification enzymes can contribute to differences in cancer sensitivities (Fig 2a)

A model for pathways containing BRCA1/2 has several strong links to leukemias - cancers that can be induced by formaldehyde or acetaldehyde (Fig. 3). Table 1 summarizes relationships between BRCA1/2 pathways in Fig 3 and myeloid leukemias. Children born with defects on both chromosomes that affect the BRCA1/2 / Fanconi pathway are at high risk for AML. These defects include those in BRCA2 (Fanconi protein D1 and in PALB2(Fanconi protein N).

A characteristic fusion protein (BCR/ABL) is found in AML (and in CML) that interferes with the formation of nuclear FANCD2 foci (Fig. 3), but this interference can be reversed by the ectopic expression of BRCA1. In CML, BRCA1 becomes virtually undetectable [Valeri et al (2010)].

Mutations in nucleolar phosphoprotein nucleophosmin/B23 (NPM) are associated with a major subset of AML. BRCA1-BARD1 catalyzes the polyubiquitination of NPM and this may be essential for several NPM functions. The NPM gene encodes a phosphoprotein that moves between the nucleus and the cytoplasm. NPM colocalizes with BRCA1 and BARD1 in mitotic cells. The heterodimer BRCA1-BARD1 catalyzes the ubiquitination of NPM in vitro and in vivo, and BRCA1-BARD1 co-expression in cells causes NPM stabilization rather than degradation [Sato et al (2004)] Familial AML is linked to the loss of the long arm of chromosome 5 which includes the NPM gene on chromosome 5q33–34. 5q33-34 contains one or more genes that modify breast cancer risk in BRCA1 mutation carriers [Nathanson and Weber (2002)].

Biallelic Fanconi N (PALB2) mutations are associated with AML and other pediatric malignancies [Tischkowitz and Xia (2010)]. Fanconi protein A is lost in a subset of sporadic AML [Tischkowitz et al (2004)] Casorelli et al (2006) found that impaired recombination repair stimulated aPL. Quantitative real time PCR and microarray data, showed reductions ranging from 3

Table 1 Connections between BRCA1/2 containing pathways and leukemias

Leukemia	Evidence for connections to BRCA1/2 pathway	Reference
AML	Childen born with defects on both chromosomes affecting genes encoding BRCA2 or both chromosomes affecting FANCN genes are especially prone to develop AML.	Alter et al 2007, Tischkowitz et al (2010)
AML, CML	BCR/ABL fusion protein inhibits the formation of nuclear FANCD2 foci	Valeri et al 2010
AML	NPM is a substrate for BRCA1-BARD1. In AML in China, where pollution is high, NPM1 is frequently lost. NPM1 locus on chromosome 5 is part of a region that modifies breast cancer risk in BRCA1 related breast cancers.	Sato JBC 2004; Wang et al 2010; Nathanson and Weber 2002
AML	ATM mutations increase the incidence of translocations at 11q23 involving the multi-lineage leukemia gene (MLL). ATM prevents oncogenic translocations	Bredemeyer et al 2006; Sun et al, 2010
Myeloid leukemias	Frequent loss of chromosome 17 [monosomy 17] containing BRCA1 and p53	Zhu et al 2008
Acute promyelocytic leukemia (APL)	PML fusion protein with retinoic acid receptor causes loss of PML protein function. PML is essential for proper localization of RAD51 in nuclear foci and efficient homology directed repair. PML also participates in localizing BRCA1.	Boichuk 2011
Acute promyelocytic leukemia (APL)	BRCA1 expression is reduced 3 to 14.3 fold in APL	Casorelli et al 2006
Fanconi anemia associated cancers especially AML	The model in Fig 3 shows how Fanconi proteins are required for activities of BRCA1 and BRCA2.	

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to14.3 fold in MSH6, MLH1, BRCA1 and RAD51 expression in all APL samples.

The promyelocytic leukemia protein (PML) is a tumor suppressor. At first this function seemed restricted to leukemia but was soon extended to solid tumors. PML is critical for forming nuclear bodies with important functions in transcription, apoptosis, DNA repair and antiviral responses. BRCA1 colocalizes with these nuclear bodies which may be essential for chromatin remodeling [Luciani et al (2006)]. The gene is often involved in the translocation with the retinoic acid receptor alpha gene. This results in loss of PML function and is associated with acute promyelocytic leukemia (APL). PML expression is also lost in some solid tumors, the loss correlating with tumor progression. PML is critical for proper localization of the essential repair protein Rad51 in nuclear foci, and for efficient homology-directed repair. In cells expressing SV40 large T antigen, Rad51 foci depend on PML (Fig. 3). PML participates in localizing, or otherwise regulating, additional factors with links to the pathway in Fig. 2. These include BLM, MRN, RPA and BRCA1 [Boichuk et al, 2011].

In myeloid leukemias, chromosome 17 (containing BRCA1) is frequently lost or involved in complex chromosomal abnormalities including balanced translocations involving the BRCA1 locus [Zhu et al (2008)]. Some pathogenic mechanisms in leukemias may be related to those in hereditary breast cancers.

Mutations in pathways depending on BRCA1/2 genes increase risks for myeloid leukemia.

Associations between BRCA1/2 mediated pathways and myeloid leukemia were independently tested against mutation related risks for myeloid leukemia. This association is especially strong for homozygous or biallelic mutations in BRCA2 (Fanconi protein D1). Six children with biallelic BRCA2 mutations all developed leukemia at median age 2.2 years, with 4 of 6 developing acute myeloid leukemia (AML) [Wagner et al. (2004)]. Biallelic BRCA2 mutation patients have a 79% cumulative probability of leukemia (primarily AML) by age 10 years [Alter et al. ((2007)] (Table 2).

Homozygous or biallelic mutations in BRCA1 are incompatible with human life but heterozygous BRCA1 mutations are well known. Carriers of heterozygous mutations in either BRCA1 or BRCA2 have increased risks for myeloid leukemia. Rows 3 through 16 of Table 2 summarize risks for myeloid leukemia from 14 studies of known/potential heterozygous BRCA1/2 mutation carriers or individuals eligible for mutation testing. Most studies reported elevated risks for leukemia or other hematopoietic cancers. Risks may be even greater because none of the heterozygote studies included populations that had all tested positive for mutation and very ill cancer patients may have been lost to follow up.

Mutations in Fanconi anemia genes. Fanconi anemia is an inherited cancer condition caused by inactivation of one of 13 Fanconi anemia complementation groups. In Fanconi anemia patients, summary relative risks for AML were 703.3 [363.7–1354.5] [Friedenson (2007)]. This suggests that functional Fanconi proteins are essential to prevent generation of cancer stem cells and AML [Tischkowitz et al. (2004)]. Few stringent genotype–phenotype connections have emerged for Fanconi anemia. Other genes and environmental factors may modify the phenotype [Neveling et al. (2009)].

Mutations in Fanconi genes contribute to a subset of sporadic AML [Lensch et al. (2003), Condie et al. (2002), Xie et al. (2000)]. In heterozygous carriers, lymphocytes show increased sensitivity to mutagens, but are not blocked in G2 phase as in full Fanconi Anemia [Rischewski et al (200), Mohseni et al. (2009]. Heterozygous mutation in the Fanconi J gene prevents the encoded helicase

Table 2. Risks of leukemia and oral cavity cancers as cancers following breast, ovarian or fallopian tube cancer in proven or potential BRCA1/2 mutation carriers

Row number, Study population and reference	Mutation test status	Risk measurement for leukemias [Confidence interval]
1. 6 children with biallelic BRCA2 mutations [Wagner (2004)].	Biallelic BRCA2 mutations (compound heterozygotes)	All developed leukemia at median age 2.2 years. 4 of 6 AMLs
2. Review of 27 biallelic BRCA2 mutation patients [Alter (2003)].	Biallelic BRCA2 mutations (compound heterozygotes)	79% cumulative probability of leukemia (primarily AML) by age 10 years
3. First breast cancer age <45 in 6958 Connecticut women. [Harvey & Brinton, 1985]	Potential mutation carriers eligible for mutation testing	Acute non-lymphocytic leukemia as 2nd cancer O/E=2.9 at 1-4 years and 6.4 at 5-9 years
4. Breast cancer patients, age 35-49 from 26,617 primary female breast cancers [Teppo et al, 1985]	Potential mutation carriers eligible for mutation testing	Subsequent leukemia (excluding CLL) RR= 3.21 p<.01
5. Female breast cancer surviving >= 10 years (selects 11,273 younger patients) [Ewertz & Mouridsen, 1985]	Potential mutation carriers eligible for mutation testing	Acute non-lymphocytic leukemia as a 2nd cancer RR=2.3
6. 2813 women with 2 breast or ovarian cancers in Thames Cancer Registry. [Evans et al, 2001b]	Potential BRCA1/2 mutation carriers eligible for mutation testing	Myeloid leukemia RR=5.04 [1.85-11.0]
7. 82,520 Women with breast cancer age <=45 in 13 cancer registries. [Mellemkjaer et al, 2006]	Potential mutation carriers eligible for mutation testing	Myeloid Leukemia SIR = 3.02 (2.32–3.85) Leukemia SIR = 2.16 (1.78–2.59).
8. 2,084 Women with primary fallopian tube cancer from 13 cancer registries [Riska et al, 2007]	Probable BRCA1/2 mutation carriers.	Non-lymphoid leukemia RR=3.7 (1.0-9.4)
9. 2nd cancer after Breast Cancer<50. from 32, 799 patients in Thames Cancer Registry. [Evans et al, 2001a]	Potential BRCA1/2 mutation carriers eligible for mutation testing	Myeloid leukemias RR=2.31 [1.52-3.51]
10. 2nd cancer after male breast cancer [Hemminki et al, 2005]	Men at high risk for being (BRCA2) mutation carriers eligible for mutation testing	Myeloid leukemia RR=3.98 [1.46 – 8.67] 1-9 yrs of follow up. RR=3.42 [1.47-6.73] for all periods
11. *534* First degree relatives of BRCA1 probands with ovarian cancer [Risch et al, 2006]	Tested BRCA1 heterozygotes or potential carriers eligible for testing	Leukemias, lymphomas, etc RR=3.7 (1.5 to 9.5)
12. 7/98 multiple primary cancer fami lies with a BRCA1 mutation and 8/98 multiple primary cancer fami lies with a BRCA2 mutation [Shih et al, 2000]	Known BRCA1 and BRCA2 mutation carriers	20% of leukemias in the families occurred in BRCA1 and BRCA2 mutation carriers.
13. 3678 women, 50 men. 1st degree relatives of BRCA2 mutation carriers or of breast or ovarian cancer patients [Breast cancer linkage consortium, 1999]	471 BRCA2 carriers, 390 noncarriers, and 2186 unknown BRCA2 carrier status	Leukemia RR= 1.12 [0.30–4.25]
14. 11847 individuals from 699 families segregating a BRCA1 mutation [Thompson et al, 2002]	18.9% (2245) tested BRCA1 carriers, 9.3% (1106) tested negative, 71.7% (8496) untested.	Leukemia RR = 0.88 [0.37 to 2.14] p=.83
15. 1811 male and female family mem bers [Van Asperen et al, 2005]	50% probability BRCA2 mutation from 139 BRCA2 families.	Leukemia RR= 1.5 [0.5 to 3.5]
16. 728 males & females (BRCA2). 1145 males & females (BRCA1) [Johannson et al, 1999]	From families with an identified BRCA2 or BRCA1 mutation	Acute leukemia SMR=1.54 [0.04±8.59] (BRCA2). 1.01 [0.03±5.62] (BRCA1)

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Studies of heterozygotes or potential heterozygotes listed in Table 2

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

Evans H, Lewis C, Robinson D, Bell C, Moller H, Hodgson S. (2001a). Incidence of multiple primary cancers in a cohort of women diagnosed with breast cancer in southeast England. Brit J Cancer 84: 435-440

Evans H., Lewis, C., Robinson, D. et al. (2001b) Cancer risks in women with 2 breast or ovarian cancers: clues to genetic cancer susceptibility. Int J. Cancer 94: 758-9

Ewertz, M. & Mouridsen, H. Second cancer following cancer of the female breast in Denmark, 1943-80. Natl Cancer Inst Monogr. 1985; 88:325-9

Harvey EB and Brinton LA. Second cancer following cancer of the breast in Connecticut, 1935–1982. Natl Cancer Inst Monogr 1985; 68, 99–109

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.

Johannsson O, Loman N, Moller T, Kristoffersson U, Borg A, Olsson H. Incidence of malignant tumors in relatives of BRCA1 and BRCA2 germline mutation carriers (1999). Eur J Cancer 35:1248–57

Mellemkjaer L, Friis S, Olsen JH, Scélo G, Hemminki K, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride ML, Kliewer EV, Tonita JM, Kee-Seng C, Pompe-Kirn V, Martos C, Jonasson JG, Boffetta P, Brennan P. (2006). Risk of second cancer among women with breast cancer. Int J Cancer 118(9):2285-92.

Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Fan I, Tang J, Li S, Zhang S, Shaw PA, Narod SA. (2006) Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst. 98(23):1694-706.

Riska A, Pukkala E, Scélo G, Mellemkjaer L, Hemminki K, Weiderpass E, McBride ML, Pompe-Kirn V, Tracey E, Brewster DH, Kliewer EV, Tonita JM, Kee-Seng C, Jonasson JG, Martos C, Boffetta P, Brennan P. (2007) Second primary malignancies in females with primary fallopian tube cancer. Int J Cancer 120(9):2047-51.

Shih H, Nathanson K, Seal S, Collins N, Stratton M, Rebbeck T and Weber B. (2000). BRCA1 and BRCA2 mutations in breast cancer families with multiple primary cancers. Clin Cancer Res 6, 4259-64.

Teppo L, Pukkala E and Saxen E. (1985) Multiple cancer – an epidemiological exercise in Finland. J Natl Cancer Inst 75: 207–217.

Thompson D, Easton DF; Breast Cancer Linkage Consortium (2002). Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst. 94(18):1358-65

van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, Hoogerbrugge N, Verhoef S, Vasen HF, Ausems MG, Menko FH, Gomez Garcia EB, Klijn JG, Hogervorst FB, van Houwelingen JC, van't Veer LJ, Rookus MA, van Leeuwen FE; Netherlands Collaborative Group on Hereditary Breast Cancer (HEBON). (2005) Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet. 42(9):711-9.

Footnotes: *NR= Not reported. Confidence intervals are given in brackets. #RR=1.1 for mouth cancer. * Head/neck and vocal cord cancer reported as "other primary tumors." ** 2 nose cancers reported in addition. *** Nasal sinus cancer reported but RR=0.15 for buccal cavity and pharynx cancer.*

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from unwinding DNA [Wu et al. (2010]], suggesting one mechanism.

ATM mutations. ATM may prevent oncogenic translocations by preventing excessive loading of recombinational repair proteins onto translocation breakpoint cluster regions ("hotspots") [Bredemeyer et al. (2006)]. Chromosomal translocations involving the MLL (Multi Lineage Leukemia) gene on chromosome 11q23 are very common in infantile and secondary leukemias. The ATM gene is near MLL and ATM deficiencies increase the incidence of 11q23 translocations in a fibroblast cell line and fluorescence in situ hybridization analysis shows split MLL gene signals are more numerous in cells after DNA damage.

The MLL gene is one of the few genes with multiple translocation partners in leukemias. More than 70 MLL translocations have been reported in de novo and therapy related AML or ALL. A strong non-homologous end joining repair signature exists at all of these chromosome translocation breakpoint junctions. Most other chromosome translocations in leukemia have no consistent homologous sequences at the breakpoints [Zhang and Rowley, 2006].

Most breakpoints occur within an 8.3 kb breakpoint region within exons 7-13 of the MLL gene. MLL rearrangements at the 11q23 breakpoint cluster region are strongly linked to AML, representing a WHO subtype found in approximately 15% of patients with AML and ALL.

There are isolated reports of AML associated with ATM mutation, but malignancies in the lymphoid branches of hematopoetic cell development are common. Lymphoid malignancies may represent competing risks.

Risks for cancers of the oral cavity in mutation carriers. Acetaldehyde is strongly suspected in cancers of the upper aerodigestive tract. Formaldehyde is linked to nasopharyngeal and sinonasal cancers [Baan et al. (2009), National Toxicology Program (2010)]. The annual incidence of nasal tumors in the United States is < 1 in 100,000 people per year. Such rare outcomes are difficult to study due to a lack of statistical power. Searches in homozygous mutation carriers however found that cancers of the oral cavity are the most frequent solid tumors in Fanconi homozygotes with relative risk >200 times normal [Alter et al. (2007)]. For heterozygotes or potential heterozygotes, the disease may be too rare to allow a sufficient sample size to properly evaluate risks.

Formaldehyde, acetaldehyde and leukemias. Formaldehyde is now a proven cause of human myeloid leukemia. Myeloid leukemia develops at 2 – 5.9 ppm formaldehyde in air.

Myeloid leukemia was a prototype in formulating the cancer stem cell theory. Search results in model systems show a connection between formaldehyde and stem cell damage. As measured by increases in characteristic stem cell pathways, formaldehyde activates and damages stem cells during carcinogenesis. [Andersen et al. (2010)]. Other model studies show that ethanol can induce oxidative DNA damage via the metabolism of ethanol by the ADH1B/ALDH2 pathway[Yan et al. (2011)]. Lipid oxidation products are increased in myeloid leukemia. Some of these products resemble crotonaldehyde, an intermediate in acetaldehyde metabolism (Fig 2). Rats fed acetaldehyde in their drinking water have increased incidence of leukemias, lymphomas and the benign breast tumors fibroadenomas and fibromas.

Searches of epidemiologic studies found potential associations between acetaldehyde and myeloid leukemias. Alcohol consumption during pregnancy may increase risk for childhood AML (Latino-Martel et al (2010). Odds Ratios of 10.48 [2.8- 39.1] were reported for leukemia in children born to women who drank during the second or third trimester of pregnancy [Shu et al (1996)].

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Acetaldehyde, formaldehyde and breast cancer risks

Acetaldehyde forms during alcohol metabolism (Fig. 2a) and the system can be saturated. Overwhelming natural metabolic systems by excess drinking or inheriting variant combinations of enzymes in metabolic pathways can raise acetaldehyde levels. Acetaldehyde alone is a complete carcinogen, at least in rodent nasal epithelium where it causes nasal tumors and squamous cell carcinomas. Many studies have found that acetaldehyde increases the frequency of sister chromatid exchanges and aberrations in mammalian cells. Exposure of DNA to acetaldehyde results in a DNA interstrand cross link and other lesion responsible for carcinogenic properties of crotonaldehyde. Histones and naturally occurring polyamines facilitate the formation of these lesions [Brooks, Theravathu.(2005); Sako et al (2003)].

Acetaldehyde detoxification can deplete antioxidant defenses and generate oxygen species that cause additional complex DNA damage. Acetaldehyde is a very good substrate for other enzymes present in breast cells: xanthine oxidoreductase (XOR) and aldehyde oxidase (AOX) [Shaw et al (1989), Dumitrescu and Shields (2005)]. As they convert acetaldehyde to acetate, both these enzymes can generate reactive oxygen species i.e. superoxide, hydroxy radical and hydrogen peroxide. Both enzymes are present and regulated in breast tissues. Decreased xanthine oxidoreductase is associated with worse prognosis in ovarian carcinoma Breast cancers that lack cytoplasmic XOR have about a 2.5 greater risk of metastases than those with strong XOR expression [Linder et al. (2005)]. The generation of free radicals is also associated with the reaction catalysed by cytochrome P-4502E1. [Jelski et al (2006)] Breast tissue can convert ethanol to acetaldehyde and free radicals [Maciel et al (2004)].

Model system searches found several studies report that acetaldehyde causes complex DNA adducts and damage that requires BRCA1/2 pathway mediated repairs [Marietta et al 2009; Nakano et al (2003, 2009)]. Acetaldehyde increased chromosomal aberrations in Fanconi anemia cells much more than in normal cells [Obe et al (1979)]. Meanwhile ethanol may suppress BRCA1 levels [Fan et al (2000)].

Acetaldehyde occurs in breast milk and breast feeding mothers transfer it to infants. An exaggerated blood acetaldehyde response that has been reported after ethanol administration to pregnant rats begins a much larger alteration during lactation. At the end of pregnancy, there is a 4-fold increase in the acetaldehyde above nonpregnant values after an intragastric dose of 3 g/kg ethanol. During gestational days 1 to 17, the levels did not differ. After delivery, the exaggerated acetaldehyde response to ethanol was increased, producing acetaldehyde concentrations 15-fold greater than in nonlactating controls [Gordon et al (1985)].

Over 100 published studies find that drinking alcohol increases breast cancer risk. Search results found epidemiologic studies consistent with increases in breast cancer risk in BRCA1/2 mutation carriers caused by acetaldehyde. Four studies in Table 3 show early onset breast cancer associated with alcohol genotypes that allow rapid production or accumulation of acetaldehyde. One additional result [Moorman et al (2011)] shows that women who are potential or known mutation carriers get breast cancer sooner if they consume alcohol.

Women with an efficient alcohol dehydrogenase produce higher levels of acetaldehyde. The relationship between ADH1C polymorphism and cancer only can be studied in populations with significant alcohol consumption [Seitz and Becker (2007)]. Mitochondrial damage in this population may contribute to elevateld acetaldehydelev-

Table 3 Epidemiologic studies of acetaldehyde/alcohol and early onset breast cancers

Reference	Patients	Results
Freudenheim et al (1999)	134 premenopausal, 181 postmenopausal breast cancer patients an efficient form of ADH vs controls with similar alcohol intakes	OR=3.6[1.5-8.8] premenopausal breast cancer
Vachon et al (2001)	Daily drinkers who were first degree relatives of breast cancer probands	RR=2.45 [1.2-5.02]
Terry et al (2006)	>1000 breast cancer patients and fast alcohol metabolizers sing data from the Long Island, NY Breast Cancer Study Project.	Premenopausal risk OR=2.9[1.2-7.1] for 1-2 drinks per day
Coutelle et al (2004)	ADH1C genotype in 117 moderate alcohol consumers with breast cancer. The ADH1C*1 allele was significantly more frequent in moderate alcohol consumers with breast cancer vs. age-matched alcoholic controls without cancer (62% vs. 41.9%)	Women with the ADH1C*1,1 genotype were 1.8 times more at risk for breast cancer than those with another genotype
Moorman et al. (2011)	Females age >=20 diagnosed with breast cancer and tested for BRCA1/2 mutations. 283 BRCA1 and 204 BRCA2 positive cases	BRCA1/2 mutation carriers got breast cancer up to nearly four years younger if they consumed alcohol

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els. Negative results have been reported when very high percentages of breast cancer patients (>=70%) are non-drinkers or light drinkers.

Evidence from breast cancer clusters on Long Island, New York also suggests that alcohol may increase risk in mutation carriers. Women who lived in this area and developed breast cancer were more likely to use alcohol and to have risk factors associated with BRCA mutations. BRCA mutation related risk factors included Ashkenazi Jewish heritage and a family history of breast cancer.

Adding risks from BRCA1/2 pathway mutations to those from rapid alcohol metabolism and estrogen elevation may make some women at especially high cancer risks from alcohol use. Acetaldehyde elevation in drinkers associates with high estrogen menstrual phases and with oral contraceptive use [Eriksson et al (1996), Cannizzaro et al (2010)]. The enzyme encoded by ADH1C not only converts alcohol to acetaldehyde but may also participate in estrogen metabolism. In premenopausal women alcohol associates with higher blood estrogen levels although some studies found this only occurred in women using oral contraceptives. Even small amounts of alcohol given to healthy women led to an increase in estradiol of 27-38% when alcohol was detectable in the blood [Coutelle et al (2004)].

In contrast to evidence linking alcohol and acetaldehyde to breast cancer, similar links to formaldehyde are almost non-existent. Greater numbers of DNA-protein cross-links were found in the white cells of breast cancer patients than in matched controls [Wu et al. (2002)]. Higher activity of ALDH1 (cytosolic) aldehyde dehydrogenase in BRCA1 breast stem cells and hematopoietic cancer stem cells suggests less ability to remove aldehydes and greater susceptibility to mutagenic

effects. Formaldehyde in the environment has been positively associated with breast cancer risk [Coyle et al. (2005)].

Mutation carriers have widely varying cancer risks. Female mutation carriers have high risks for early onset breast /ovarian cancer as a group but many stiudies were found showing individual risks within this group vary greatly. There is no single risk associated with BRCA1 or BRCA2 carrier status [Begg et al. (2008)]. Defective BRCA genes increase risks for cancers in organs other than breast and ovary but individual mutation carriers again differ greatly [Friedenson (2005)]. These results implicate an increased susceptibility in organs exposed to environmental carcinogens and/or deficits in additional genes [Friedenson (2010a)].

There are unrelated examples of inherited cancer associated conditions that have increased susceptibility to environmental carcinogens. Common findings are increased sensitivity to cancer associated infections, to radiation, and to chemical carcinogens. This shows that the phenomenon of increased sensitivity to environmental carcinogens formaldehyde and acetaldehyde are probably representative of a broad general phenomenon.

Discussion

Treatment related risk factors for myeloid leukemia. The pathway connections in Fig. 3 suggest that any cause of myeloid leukemia should be over represented because inherited BRCA1/2 pathway defects predispose to myeloid leukemias. Adding cancers related to known infectious agents stresses the influence of enviromental carcinogens.

However risks also include treatment related risks for breast cancer due to chemotherapy and radiation treatment. The lack of data separating risk factors from treatment risks makes it difficult to determine how much of the excess risks might be associated with treatment. This is especially difficult because the median age for diagnosis of AML is 67. Myeloid leukemias therefore normally occur after early onset breast cancers. Early onset breast cancer patients treated with certain chemotherapy drugs are more likely to develop AML. Some of the drugs linked with these secondary (treatment related) leukemias include mechlorethamine, procarbazine, chlorambucil, melphalan, etoposide, teniposide and cyclophosphamide. Combining these drugs with radiation therapy further increases the risk. [Casorelli et al (2003)].

Several publications in Table 2 addressed this issue directly or provide some data that does. Hemminki et al (Table 2) noted that there was no trend for increasing risk for myeloid leukemia with follow up time. The first chemotherapy regimen for breast cancer was not published until 1975 with large trial results appearing in 1976 [DaVita and Chu (2008)]. Three 1985 studies in Table 2 include patients diagnosed with breast cancer before adjuvant chemotherapy became widely used. In comparison to later studies, the three pre-chemotherapy studies in Table 2 do not show substantially less risk for AML than the later studies. In the Harvey and Brinton study, women over 55 had no excess risk for any second cancer while women younger than 55 still had over 3 times the risk for myeloid leukemia. Neither group was likely to receive routine chemotherapy. Teppo et al (Table 2) found no difference vs age in subsequent new primary cancers in 1953-79 in any age group. Observations of approximately the same risk for AML before and after 1975 is not compatible with the fact that chemotherapy was given to a larger proportion of breast cancer patients during later periods [Table 2, Mellemkjaer, et al (2006) Evans et al, (2001a)]

AML occurs with virtual certainty in children and infants with biallelic mutations in BRCA2. AML also occurs at very young ages in Fanconi anemia patients, before any chemotherapy or radiation has been given. Moreover defects in pathways requiring normal BRCA gene function are associated with other hematopoietic

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malignancies that are not generally considered to be therapy related [Friedenson, 2007].

A few more recent studies in Table 2 show no excess risk for myeloid leukemia, consistent with environmental or additional genetic variation. Although some platinum cheotherapy did significantly raise risks for myeloid leukemias, relative risks for myeloid leukema these risks are only sightly higher than the other studies [Table 2 Riska et al (2006)].

Radiation therapy. Therapeutic doses of targeted field radiation cause very little or no increased risk of myeloid cancers. This is consistent with myeloid stem cells being more radiation resistant than non-stem cells.

Despite younger ages, breast cancer patients with BRCAI/2 mutations present at a similar stage, display a normal acute reaction to radiotherapy and have a similar prognosis compared to sporadic breast cancer patients [Gaffney et al (1998)]. An increased risk of radiation therapy related-AML is largely confined to young women with stage III breast cancer, (spread to lymphoid tissue). These patients are more likely to receive radiation in some combination with cytotoxic chemotherapy. In stage I disease, radiation is given alone and there is very little excess risk for AML [Martin et al, 2009]. Harvey and Brinton (1985) found only minor differences in AML risks for women given radiotherapy vs those who were not.

Activities of detoxification pathways may further stratify risks. High levels of alcohol consumption may be necessary for carcinogenesis because studies with very few heavy drinkers were inconsistent with these results. Other confounding factors include known genetic polymorphisms that affect activities of alcohol metabolizing enzymes and behavior. Activity of alcohol and aldehyde dehydrogenase enzymes should further stratify risks among mutation carriers.

Excess acetaldehyde (e.g. from heavy drinking) that overwhelms alcohol metabolism may contribute to the generation of cancer stem cells in mutation carriers [Friedenson (2010a)]. Acetaldehyde dehydrogenase has even served as a marker that has been used to help identify cancer stem cells in cancers typically associated with BRCA mutation - breast, pancreatic and prostate cancer.

Results here imply that carcinogens and differing routes of exposure at different stem cell activities are major sources for tissue specificity of cancer. Exposure to mutagens from alcohol metabolism occurs primarily in the digestive tract and liver but acetaldehyde, alcohol and detoxification enzymes all occur in the breast. Inherited differences in the intrinsic ability to metabolize alcohol or to detoxify other carcinogens contributes to determining the organs where cancer occurs. Further studies of relationships among genetic inheritance, cancer stem cells and environmental carcinogens are needed.

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