BJC

British Journal of Cancer (2016) 115, e2 | doi: 10.1038/bjc.2016.192

Comment on 'The incidence of leukaemia in women with *BRCA1* and *BRCA2* mutations: an International Prospective Cohort Study'

Bernard Friedenson*,[1]

[1]Department of Biochemistry and Molecular Genetics, University of Illinois at Chicago, Chicago, IL, USA

Sir,

It is important to identify breast cancer patients at undue risk for leukaemia associated with breast cancer chemotherapy to measure risks *vs* benefits of chemotherapy. Iqbal *et al* (2016) conclude that although leukaemia in BRCA2 carriers is primarily caused by breast cancer chemotherapy, it is so rare that BRCA mutation carriers can be treated according to standard protocols. However there are multiple confounders in determining risks; and leukaemia in breast cancer patients can be caused by biological factors that go beyond chemotherapy.

All patients with leukaemia had breast cancer in the study (Iqbal *et al*, 2016) but they all had different BRCA1 or BRCA2 mutations. Three breast cancer patients with leukaemia had deletions that cause major disruption in the activity of the BRCA1 or BRCA2 gene. Two of the three died. Complete inactivation of the BRCA2 gene occurs by germline mutations in some children. Of seven children with biallelic BRCA2 (FANCD1) mutations, at least five were diagnosed with childhood leukaemia before age 6 (Wagner *et al*, 2004). All six children with a mutation in IVS7 of the BRCA2 gene were diagnosed with leukaemia before age 3 (Alter, 2014). In a larger sample of 36 patients, 17 patients developed leukaemia, mostly acute myeloid leukaemias (AML) (Alter, 2014).

A total of 18 Fanconi anaemia proteins participate in pathways containing BRCA1 and BRCA2, and hereditary defects in some of the Fanconi proteins associate with very high risks for leukaemia (e.g. 20% by age 40) (Alter, 2014). Meta-analyses found the combined relative risks (confidence intervals) that a Fanconi anaemia patient will develop: AML as 703 (364–1355); leukaemia before age 15 as 170.3 (96.5–300.5); and the precancerous condition myelodysplastic syndrome as over 17 000 (Friedenson, 2007). These results show that BRCA1 and BRCA2 pathways are essential to prevent haematopoietic cancers.

The study cohort (Iqbal *et al*, 2016) was inadvertently selected for the ability to survive their mutation so the BRCA mutation carriers who participated were less likely to have mutations and environment factors serious enough to predispose to either breast cancer or leukaemia. In fact, 56% of the mutation carriers (4040 out of 7243) did not have breast cancer. As the authors note, 30% of the study group was lost to follow-up (Iqbal *et al*, 2016) and may include those most likely to have died from breast cancer or leukaemia.

Elevated leukaemia risks were not found for BRCA1 mutation carriers (Iqbal *et al*, 2016), but chemotherapy is known to interfere with BRCA1 expression by inactivating the gene promoter (Scardocci *et al*, 2006). Most primary AML cell lines have low BRCA1 expression (Faraoni *et al*, 2015). Among 47 survivors of breast cancer who developed leukaemia attributed to therapy, mutations in BRCA1 exceeded mutations in BRCA2 (6% *vs* 4%) (Churpek *et al*, 2016). From 1975 to 1978, chemotherapy meant melphalan or mechlorethamine, but later treatment used cyclophosphamide, which is less likely associated with AML (Curtis *et al*, 1992). Therefore, differences in treatment protocols (Iqbal *et al*, 2016) and the dates of treatment are potential confounders.

The length of follow-up time after chemotherapy ranged from 1.0–19.5 years (Iqbal *et al*, 2016). The standardised incidence ratio (SIR) for AML $\geqslant$10 years. after breast cancer chemotherapy is about the same as in the general population in SEER registries: SIR $=1.53$ (0.97–2.29) (Morton *et al*, 2013). The risk of AML at 1-4.9 years after chemotherapy for unselected patients is similar to SIR values for BRCA2 carriers: SIR $=8.6$ (7.32–10.05) (Morton *et al*, 2013) *vs* SIR $=8.11$ (2.06–22.07) (Iqbal *et al*, 2016), respectively. Breast cancer stage and ethnic groups are further potential confusing factors. Non-Hispanic white women and Hispanic women with stage I breast cancer have leukaemia risks after chemotherapy similar to a control population (Calip *et al*, 2015). Black women and Pacific Islanders with stage III breast cancer have leukaemia risks after chemotherapy (Calip *et al*, 2015) that are similar to those reported for BRCA2 mutation carriers (Iqbal *et al*, 2016).

Despite such potential alternate explanations, direct genomic and structural evidence supports the idea that leukaemias and other immune system cancers have associations with breast cancer that go beyond chemotherapy. Myeloid cells (macrophages) can constitute over half the mass of cells in some breast cancers (Lewis and Pollard, 2006), so mutations found in myeloid leukaemias are also found in breast cancers. T-cell leukaemias caused by the known leukaemia/lymphoma virus HTLV-1 (Kataoka *et al*, 2015) were compared with a reference set of breast cancers (Banerji *et al*, 2012), and showed that 35% (104 out of 301) of exome genes mutated in leukaemias are also mutated in breast cancers. Genes mutated in the same breast cancer genomes (Banerji *et al*, 2012) were also compared with genes recurrently mutated in eight genomes from primary AML. In AML, 28 different genes are recurrently mutated and presumably linked to AML pathogenesis (Ding *et al*, 2012). Nine (32%) of the 28 genes are also mutated in the reference breast cancers but the similarities extended further, suggesting an even stronger relationship. For example, WAC and DCLK1 were recurrently mutated genes associated with AML relapse (Ding *et al*, 2012) and were also mutated in some breast cancer genomes. Genes with functions similar to at least another 7 out of 28 (25%) additional recurrently mutated AML genes were also mutated in the breast cancers. Most breast cancer mutations occurred in genes with some connection to infection and immunity (Friedenson, 2015). At least 58 mutated genes were specifically related to leukaemias, including six multi-lineage leukaemia genes. Three of eight genes (37.5%) recurrently mutated in acute promyelocytic leukaemia were mutated in breast cancers (STAG2, SMC1A and MYCBP2) (Ibanez *et al*, 2016).

Convincing evidence associates human papilloma virus (HPV) (Glenn *et al*, 2012; Simoes *et al*, 2012) with some breast cancers. Genes that encode for pathways mediated by BRCA1, BRCA2 and Fanconi anaemia gene products are essential for immunity to clear HPV infection and to prevent replication of this dangerous pathogen (Hoskins *et al*, 2012). High percentages of genes damaged by mutation in BRCA1- and BRCA2-associated breast cancer involve immune responses or other protective functions (Friedenson, 2013; Friedenson, 2014; Friedenson, 2015). Human papilloma viruses interfere with multiple immune-associated responses (Lee *et al*, 2006; Deligeoroglou *et al*, 2013; Iijima *et al*, 2013; Sanchez-Reyes *et al*, 2014; Tummers and Burg, 2015) and cause major chromosome aberrations in human peripheral blood lymphocytes (Paz-y-Mino *et al*, 1992; Alvarez-Rosero *et al*, 2008). Human papilloma viruses are the established cause of cervical cancer. Chemotherapy given for cervical cancer in the presence of HPV infection increases leukaemia risk close to the level reported in BRCA2-associated breast cancers: SIR $=7.29$ (2.67–15.86) (Morton *et al*, 2013)

Macrophages then lymphocytes have been implicated as essential first and second intermediates, respectively, in breast infection by some viruses that have been associated with breast cancers. Immune cells become reservoirs that deliver such cancer-associated infections to the breast (Domenech *et al*, 2000; Zur Hausen, 2009; Holland and Pogo, 2012). Breast duct structures reveal integrated resident cells from the immune system (Degnim *et al*, 2014; Gulbahce *et al*, 2014) and breast cancers contain infiltrates with large numbers of macrophages and lymphocytes. Cancer or tumour virus infection of proliferating resident or infiltrated cells from the immune system can quickly spread to the breast and vice versa. There are clinical examples consistent with this explanation, for example, (Etkind *et al*, 2000; Salagovic *et al*, 2012).

Although a connection between BRCA mutations and leukaemia/lymphoma may cause concern in women who carry BRCA mutations, their cancers are not inevitable (Levin *et al*, 2012) and this connection may at last help us begin to understand and address the root causes of breast cancer.

ACKNOWLEDGEMENTS

I am grateful for support from the University of Illinois at Chicago.

CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

Alter BP (2014) Fanconi anemia and the development of leukemia. *Best Pract Res Clin Haematol* **27**(3-4): 214–221.

Alvarez-Rosero RE, Rodriguez-Argote J, Arboleda-Moreno YY, Munoz-Benitez SL, Sierra-Torres CH (2008) Chromosome aberrations in peripheral blood lymphocytes of high-risk HPV-infected women with HGSIL. *Environ Mol Mutagen* **49**(9): 688–694.

Banerji S, Cibulskis K, Rangel-Escareno C, Brown KK, Carter SL, Frederick AM, Lawrence MS, Sivachenko AY, Sougnez C, Zou L, Cortes ML, Fernandez-Lopez JC, Peng S, Ardlie KG, Auclair D, Bautista-Pina V, Duke F, Francis J, Jung J, Maffuz-Aziz A, Onofrio RC, Parkin M, Pho NH, Quintanar-Jurado V, Ramos AH, Rebollar-Vega R, Rodriguez-Cuevas S, Romero-Cordoba SL, Schumacher SE, Stransky N, Thompson KM, Uribe-Figueroa L, Baselga J, Beroukhim R, Polyak K, Sgroi DC, Richardson AL, Jimenez-Sanchez G, Lander ES, Gabriel SB, Garraway LA, Golub TR, Melendez-Zajgla J, Toker A, Getz G, Hidalgo-Miranda A, Meyerson M (2012) Sequence analysis of mutations and translocations across breast cancer subtypes. *Nature* **486**(7403): 405–409.

Calip GS, Law EH, Ko NY (2015) Racial and ethnic differences in risk of second primary cancers among breast cancer survivors. *Breast Cancer Res Treat* **151**(3): 687–696.

Churpek JE, Marquez R, Neistadt B, Claussen K, Lee MK, Churpek MM, Huo D, Weiner H, Bannerjee M, Godley LA, Le Beau MM, Pritchard CC, Walsh T, King MC, Olopade OI, Larson RA (2016) Inherited mutations in cancer susceptibility genes are common among survivors of breast cancer who develop therapy-related leukemia. *Cancer* **122**(2): 304–311.

Curtis RE, Boice Jr. JD, Stovall M, Bernstein L, Greenberg RS, Flannery JT, Schwartz AG, Weyer P, Moloney WC, Hoover RN (1992) Risk of leukemia after chemotherapy and radiation treatment for breast cancer. *N Engl J Med* **326**(26): 1745–1751.

Degnim AC, Brahmbhatt RD, Radisky DC, Hoskin TL, Stallings-Mann M, Laudenschlager M, Mansfield A, Frost MH, Murphy L, Knutson K, Visscher DW (2014) Immune cell quantitation in normal breast tissue lobules with and without lobulitis. *Breast Cancer Res Treat* **144**(3): 539–549.

Deligeoroglou E, Giannouli A, Athanasopoulos N, Karountzos V, Vatopoulou A, Dimopoulos K, Creatsas G (2013) HPV infection: immunological aspects and their utility in future therapy. *Infect Dis Obstet Gynecol* **2013**: 540850.

Ding L, Ley TJ, Larson DE, Miller CA, Koboldt DC, Welch JS, Ritchey JK, Young MA, Lamprecht T, McLellan MD, McMichael JF, Wallis JW, Lu C, Shen D, Harris CC, Dooling DJ, Fulton RS, Fulton LL, Chen K, Schmidt H, Kalicki-Veizer J, Magrini VJ, Cook L, McGrath SD, Vickery TL, Wendl MC, Heath S, Watson MA, Link DC, Tomasson MH, Shannon WD, Payton JE, Kulkarni S, Westervelt P, Walter MJ, Graubert TA, Mardis ER, Wilson RK, DiPersio JF (2012) Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. *Nature* **481**(7382): 506–510.

Domenech A, Goyache J, Llames L, Jesus Paya M, Suarez G, Gomez-Lucia E (2000) *In vitro* infection of cells of the monocytic/macrophage lineage with bovine leukaemia virus. *J Gen Virol* **81**(Pt 1): 109–118.

Etkind P, Du J, Khan A, Pillitteri J, Wiernik PH (2000) Mouse mammary tumor virus-like ENV gene sequences in human breast tumors and in a lymphoma of a breast cancer patient. *Clin Cancer Res* **6**(4): 1273–1278.

Faraoni I, Compagnone M, Lavorgna S, Angelini DF, Cencioni MT, Piras E, Panetta P, Ottone T, Dolci S, Venditti A, Graziani G, Lo-Coco F (2015) BRCA1, PARP1 and gammaH2AX in acute myeloid leukemia: role as biomarkers of response to the PARP inhibitor olaparib. *Biochim Biophys Acta* **1852**(3): 462–472.

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

Friedenson B (2013) Mutations in components of antiviral or microbial defense as a basis for breast cancer. *Funct Integr Genomics* **13**(4): 411–424.

Friedenson B (2014) Many breast cancer mutations parallel mutations in known viral cancers. *J Genomes Exomes* **3**: 17–35.

Friedenson B (2015) Mutations in breast cancer exome sequences predict susceptibility to infections and converge on the same signaling pathways. *J Genomes Exomes* **4**: 1–28.

Glenn WK, Heng B, Delprado W, Iacopetta B, Whitaker NJ, Lawson JS (2012) Epstein-Barr virus, human papillomavirus and mouse mammary tumour virus as multiple viruses in breast cancer. *PLoS One* **7**(11): e48788.

Gulbahce HE, Vanderwerf S, Blair C, Sweeney C (2014) Lobulitis in nonneoplastic breast tissue from breast cancer patients: association with phenotypes that are common in hereditary breast cancer. *Hum Pathol* **45**(1): 78–84.

Holland JF, Pogo BG (2012) Comment on the review by Joshi and Buehring. *Breast Cancer Res Treat* **136**(1): 303–307.

Hoskins EE, Morreale RJ, Werner SP, Higginbotham JM, Laimins LA, Lambert PF, Brown DR, Gillison ML, Nuovo GJ, Witte DP, Kim MO, Davies SM, Mehta PA, Butsch Kovacic M, Wikenheiser-Brokamp KA, Wells SI (2012) The fanconi anemia pathway limits human papillomavirus replication. *J Virol* **86**(15): 8131–8138.

Ibanez M, Carbonell-Caballero J, Garcia-Alonso L, Such E, Jimenez-Almazan J, Vidal E, Barragan E, Lopez-Pavia M, LLop M, Martin I, Gomez-Segui I, Montesinos P, Sanz MA, Dopazo J, Cervera J (2016) The mutational landscape of acute promyelocytic leukemia reveals an interacting network of co-occurrences and recurrent mutations. *PLoS One* **11**(2): e0148346.

Iijima N, Goodwin EC, Dimaio D, Iwasaki A (2013) High-risk human papillomavirus E6 inhibits monocyte differentiation to Langerhans cells. *Virology* **444**(1-2): 257–262.

Iqbal J, Nussenzweig A, Lubinski J, Byrski T, Eisen A, Bordeleau L, Tung NM, Manoukian S, Phelan CM, Sun P, Narod SA. Hereditary Breast Cancer Research Group (2016) The incidence of leukaemia in women with BRCA1 and BRCA2 mutations: an International Prospective Cohort Study. *Br J Cancer* **114**(10): 1160–1164.

Kataoka K, Nagata Y, Kitanaka A, Shiraishi Y, Shimamura T, Yasunaga J, Totoki Y, Chiba K, Sato-Otsubo A, Nagae G, Ishii R, Muto S, Kotani S, Watatani Y, Takeda J, Sanada M, Tanaka H, Suzuki H, Sato Y, Shiozawa Y, Yoshizato T, Yoshida K, Makishima H, Iwanaga M, Ma G, Nosaka K, Hishizawa M, Itonaga H, Imaizumi Y, Munakata W, Ogasawara H, Sato T, Sasai K, Muramoto K, Penova M, Kawaguchi T, Nakamura H, Hama N, Shide K, Kubuki Y, Hidaka T, Kameda T, Nakamaki T, Ishiyama K, Miyawaki S, Yoon SS, Tobinai K, Miyazaki Y, Takaori-Kondo A, Matsuda F, Takeuchi K, Nureki O, Aburatani H, Watanabe T, Shibata T, Matsuoka M, Miyano S, Shimoda K, Ogawa S (2015) Integrated molecular analysis of adult T cell leukemia/lymphoma. *Nat Genet* **47**(11): 1304–1315.

Lee BN, Follen M, Rodriquez G, Shen DY, Malpica A, Shearer WT, Reuben JM (2006) Deficiencies in myeloid antigen-presenting cells in women with cervical squamous intraepithelial lesions. *Cancer* **107**(5): 999–1007.

Levin B, Lech D, Friedenson B (2012) Evidence that BRCA1- or BRCA2-associated cancers are not inevitable. *Mol Med* **18**: 1327–1337.

Lewis CE, Pollard JW (2006) Distinct role of macrophages in different tumor microenvironments. *Cancer Res* **66**(2): 605–612.

Morton LM, Dores GM, Tucker MA, Kim CJ, Onel K, Gilbert ES, Fraumeni Jr. JF, Curtis RE (2013) Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008. *Blood* **121**(15): 2996–3004.

Paz-y-Mino C, Ocampo L, Narvaez R, Narvaez L (1992) Chromosome fragility in lymphocytes of women with cervical uterine lesions produced by human papillomavirus. *Cancer Genet Cytogenet* **59**(2): 173–176.

Salagovic J, Klimcakova L, Ilencikova D, Kafkova A (2012) Association of follicular lymphoma risk with BRCA2 N372H polymorphism in Slovak population. *Med Oncol* **29**(2): 1173–1178.

Sanchez-Reyes K, Bravo-Cuellar A, Hernandez-Flores G, Lerma-Diaz JM, Jave-Suarez LF, Gomez-Lomeli P, de Celis R, Aguilar-Lemarroy A, Dominguez-Rodriguez JR, Ortiz-Lazareno PC (2014) Cervical cancer cell supernatants induce a phenotypic switch from U937-derived macrophage-activated M1 state into M2-like suppressor phenotype with change in toll-like receptor profile. *Biomed Res Int* **2014**: 683068.

Scardocci A, Guidi F, D'Alo F, Gumiero D, Fabiani E, Diruscio A, Martini M, Larocca LM, Zollino M, Hohaus S, Leone G, Voso MT (2006) Reduced BRCA1 expression due to promoter hypermethylation in therapy-related acute myeloid leukaemia. *Br J Cancer* **95**(8): 1108–1113.

Simoes PW, Medeiros LR, Simoes Pires PD, Edelweiss MI, Rosa DD, Silva FR, Silva BR, Rosa MI (2012) Prevalence of human papillomavirus in breast cancer: a systematic review. *Int J Gynecol Cancer* **22**(3): 343–347.

Tummers B, Burg SH (2015) High-risk human papillomavirus targets crossroads in immune signaling. *Viruses* **7**(5): 2485–2506.

Wagner JE, Tolar J, Levran O, Scholl T, Deffenbaugh A, Satagopan J, Ben-Porat L, Mah K, Batish SD, Kutler DI, MacMillan ML, Hanenberg H, Auerbach AD (2004) Germline mutations in BRCA2: shared genetic susceptibility to breast cancer, early onset leukemia, and Fanconi anemia. *Blood* **103**(8): 3226–3229.

Zur Hausen H (2009) The search for infectious causes of human cancers: where and why. *Virology* **392**(1): 1–10.

*Correspondence: Dr B Friedenson; E-mail: bernief@uic.edu
Published online 26 July 2016