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Hemochromatosis and ovarian cancer

David M Robertson[†]

Evaluation of: Gannon PO, Medelci S, Le Page C et al. Impact of hemochromatosis gene (HFE) mutations on epithelial ovarian cancer risk and prognosis. *Int. J. Cancer* 128(10), 2326–2334 (2011). The frequency of two mutations (C282Y and D62H) of the hemochromatosis gene were investigated in women with ovarian cancer. A single allele mutation of the C282Y but not the H63D gene product was detected in 8–9% of women with benign ovarian tumors (n = 124) and ovarian cancers (n = 360) compared with 2.5% for controls (n = 80) representing a 4.9-fold increase in risk. With high-grade serous ovarian cancers (n = 179), the survival rate of women with a single allele C282Y mutation was reduced from 39 to 19 months. These results implicate mutations of the hemochromatosis gene in the generation and severity of ovarian cancers, which may have prognostic value.

Women's
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It is well recognized that iron is a critical nutrient playing key roles in cellular metabolism. It also plays a key role in proliferation and, as such, cancer cells utilize iron at a high rate. Iron deprivation by use of iron chelators has been shown to reduce the growth of tumors.

Iron uptake by tissues involves the transfer of iron bound to the blood-bound carrier ferritin to surface transferrin receptors prior to internalization. This uptake process is restrained by a complex of two other surface proteins, one a hemochromatosis gene (HFE) product, mutations of which are responsible for hereditary hemochromatosis and the other, β 2-microglobulin. Two HFE mutations, a cysteine to tyrosine change at amino acid 282 (C282Y) and a histidine to aspartic acid change at amino acid 63 (H63D) have been identified, which result in hereditary hemochromatosis, and this is attributed to a reduced inhibitory interaction of these mutated molecules (in particular, the C282Y mutation) with the transferrin receptor. As a consequence of these mutations there is an increase in circulating iron and iron uptake by the tissue.

It has been conjectured that excess iron is deleterious to tissues by increasing oxidative stress, and thus DNA damage, and that in hormone-dependent target organs (e.g., breast, ovary and uterus) iron uptake is regulated by the role of estradiol-sensitive intermediates. In support of this hypothesis, the dramatic increase in circulating and tissue iron levels in women after menopause [1], which inversely correlates with the reduction in circulating ovarian steroids levels, would suggest that the elevated iron levels may be contributing to the increased incidence of cancers in this late age group.

Thus, is there an increased risk of cancers in women with HFE mutations? Epidemiological studies of women with breast cancer have given

conflicting results [2,3], however, no similar studies have been undertaken with ovarian or endometrial cancer.

The objective of this study was to establish if women with the two HFE mutations have an increased risk of ovarian cancer and whether these HFE mutations have an impact on survival of women with ovarian cancer.

Summary of methods & results

The clinical group under investigation consisted of 677 consecutive patients (average 56 years) who underwent surgery for ovarian and endometrial cancers. The resulting tumors were classified based on their histopathology, tumor grade and disease into a benign cancer group (n = 124) and an epithelial cancer group consisting of low malignant potential (n = 96) and invasive (n = 264) tumors. A control group (n = 80) consisting of women who had non-neoplastic pathologies and were thus tumor free, and a group of women (n = 113) with endometrial cancer were included. The hemochromatosis genotype was determined for the C282Y and H63D mutations by individual PCR analyses.

Initially, the frequency of the two mutations was assessed in the various clinical groups. The proportion of women with one allele of the C282Y mutation in the epithelial ovarian cancer group was significantly higher (8.9%) compared with the control (2.5%, $p = 0.038$) and endometrial cancer groups (2.7%, $p = 0.019$). Benign tumors were also elevated (8.1%) but this group was not significantly different from controls. Low malignant potential and invasive tumors (together making up the epithelial ovarian cancer group) were 9.4% ($p = 0.05$) and 8.7% ($p = 0.04$), respectively. The number of homozygous carriers was too few for detailed

[†]Prince Henry's Institute of Medical Research, PO Box 5152, Clayton 3168, Victoria, Australia
Tel.: +61 395 947 901
Fax: +61 395 947 909
david.robertson@princehenrys.org

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analysis ($n = 2$). By contrast, the frequencies of the H63D mutation (in either one or both alleles) between ovarian control, benign and cancer groups were not significantly different.

The estimated risk of ovarian cancer was significantly higher for women with the C282Y mutation in the epithelial ovarian cancer groups compared with controls (odds ratio 4.88; $p = 0.018$).

The survival rate of women with the C282Y mutation was assessed by Kaplan–Meier analysis. Such women with ovarian cancer showed a decreased survival rate and this was clearly seen in the invasive ovarian cancer group where for a single C282Y allele mutation, the median survival time decreased from 33.7 months in the control group to 19.4 months in the cancer group.

By multivariate analysis, the C282Y mutation, grade of cancer and age were independently correlated with overall survival.

Discussion

Women with ovarian cancer have a higher frequency of the C282Y mutation and women with ovarian cancer with this mutation have a shorter survival time. By contrast, the H63D mutation was similarly detected in both ovarian cancer and control groups with similar survival times. The authors conclude that the presence of the C282Y mutation may increase the risk of ovarian cancer with poorer outcomes for those with ovarian cancer.

A number of hypotheses are proposed to explain these findings. One of the major tenets of the study was that those women with one C282Y allele are defective in iron uptake or storage and that as a result, the excess iron is responsible for the development and aggressiveness of the resulting tumor. In a large clinical study, C282Y heterozygotes were shown to have significantly elevated transferrin saturation values and serum ferritin levels [1], although clinically such women were not at an increased risk of iron overload. For example in the study of Beutler and Waalen [1], the serum ferritin levels in control women (53 $\mu\text{g/l}$) were slightly lower, although the difference was significant, than women with one (57 $\mu\text{g/l}$) or two (161 $\mu\text{g/l}$) C282Y alleles. A combination of one allele of both C282Y and H63D resulted in higher ferritin levels (71 $\mu\text{g/l}$). However, after menopause and attributed to the decrease in ovarian reproductive steroid levels, the levels of circulating ferritin increased twofold [4], a likely physiologically significant change that is probably

exacerbated by the presence of the C282Y mutation. It is interesting to note that two-thirds of ovarian cancers are detected in women after menopause and this association with an increase in iron uptake supports this link.

The question is then why is there not a similar relationship between the C282Y allelic frequency for women with endometrial cancer and controls? Endometrium, like the ovary, is hormonally sensitive and, in particular, estrogen sensitive. One must take into account that other factors are involved. The authors argue that problems of anemia in women with these cancers have prevented an assessment of iron levels in women with these cancers. It is interesting that a similar incidence of the C282Y mutation was observed in women with both ovarian benign tumors and cancers in this study, suggesting an ovarian rather than a cancer-specific effect.

The authors have proposed several hypotheses to explain the association of HFE mutations with ovarian cancer. The first is that iron can be considered as a carcinogen and that an elevation in iron uptake will promote the development of ovarian cancer. Its mechanism of action is the recognized capability of iron to induce oxidative stress leading to DNA damage and increased mutagenesis. The second, that HFE, as a MHC class-like molecule, is involved in antigen presentation pathways and thus has a immunological function. The presence of intratumoral T cells in ovarian cancers has been independently correlated with delayed recurrence or delayed death [5], suggesting that impairment of HFE presentation ability would facilitate cancer development. The third, is related to the processing by the cell of the mutated molecule whereby its retention by the cell can trigger the ‘unfolded protein response’ that is associated with tumor progression.

Future perspective

This study provides evidence of an association between HFE mutations and ovarian cancer. If this finding is confirmed it means that the risk of ovarian cancer by HFE mutation carriers is increased considerably from a lifetime risk of 1:48 [101] to 1:10, comparable to that observed with breast cancer, which clearly warrants further investigation. The basis for this association is not understood. Is it attributed to an increase in tissue iron loading or other aspects of HFE function? The authors conclude that larger trials are needed to confirm and extend these findings.

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Executive summary

- It is hypothesized that increased iron uptake associated with the iron storage disease hemochromatosis is also associated with a higher incidence of ovarian cancer.
- The frequency of two mutations (C282Y, H63D) in heterozygous carriers of the hemochromatosis gene was assessed in 677 women consisting of 80 controls, 124 benign, 96 with low metastatic potential and 264 women with invasive ovarian tumors.
- The proportion of women with a single allele of the C282Y mutation was significantly elevated in women with benign tumors and ovarian cancers (8–9%) compared with the control group (2.5%). This was reflected in a 4.9-fold increase in risk of developing ovarian cancer. No differences were observed with the H63D mutation.
- Survival rates for women with high-grade serous ovarian cancer with the heterozygous C282Y mutation were halved from 39 to 19 months.
- While elevated iron uptake may be considered as an ovarian carcinogen, other hypotheses related to the roles of the hemochromatosis protein in immunity and reproductive status are also possible to explain these observations.

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