BREAST CANCER IN YOUNG WOMEN FROM GENETICS TO HORMONAL THERAPY

Commissioned Training in O&G
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Dr Miranda Chan
COS, Surgery, KWH

Breast Cancer in Young Women

- Incidence
- Diagnosis problem
- Relationship to hereditary cancer, BRCA1 and BRCA2 mutation
- Breast cancer in pregnancy
- Surgical Options
- Chemotherapy
- Radiotherapy

Hong Kong Cancer Registry

Incidence Rate for all ages 2002-2011

<table>
<thead>
<tr>
<th>Rank</th>
<th>Site</th>
<th>No. in 2011</th>
<th>No. in 2003 (Rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Colorectum</td>
<td>4,450</td>
<td>1,284 (2)</td>
</tr>
<tr>
<td>2</td>
<td>Lung</td>
<td>4,464</td>
<td>5,536 (3)</td>
</tr>
<tr>
<td>3</td>
<td>Breast</td>
<td>1,446</td>
<td>2,016 (8)</td>
</tr>
<tr>
<td>4</td>
<td>Liver</td>
<td>1,854</td>
<td>1,617 (6)</td>
</tr>
<tr>
<td>5</td>
<td>Prostate</td>
<td>1,644</td>
<td>755 (7)</td>
</tr>
</tbody>
</table>

- Colorectal cancer has overtaken lung cancer for the first time to become the most common cancer in Hong Kong.
- Most of the increase was attributed to the growing number of increase in breast, thyroid and ovarian cancers in women and prostate cancer in men.
Breast cancer in young women

- Around 600 under 40yrs
- Modest increase in incidence in past 10 yrs
- More significant increase in age group 40 yrs or above
- Target group of mammogram screening: 40+

Breast Cancer in Young Women

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- Relationship to hereditary cancer, BRCA1 and BRCA2 mutation
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- Chemotherapy
- Radiotherapy
Diagnosis in young women

- Dense breast parenchyma lower the sensitivity of mammograms
- Screening mammogram is not applicable
- MRI is specific but expensive
- Ultrasound is useful but of inferior sensitivity
- Patient usually presents with palpable mass

MRI

- Sensitivity ~100%; Specificity: 60%
- Rapid initial enhancement after gadolinium injection
- Dense breast in young patients
- Invasive lobular carcinoma
- Occult breast primary with positive axillary lymph node
- Define extent of disease before lumpectomy

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Life time risk of breast cancer according to family history

<table>
<thead>
<tr>
<th>Relatives with breast cancer</th>
<th>Increase in risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother or sister diagnosed over 35</td>
<td>2.5x</td>
</tr>
<tr>
<td>Mother or sister diagnosed under 35</td>
<td>1.5-2.0x</td>
</tr>
<tr>
<td>2 first degree relatives, average age at diagnosis &lt;55</td>
<td>2.5-3.0x</td>
</tr>
<tr>
<td>2 first degree relatives, average age at diagnosis &gt;55</td>
<td>1.5-2.0x</td>
</tr>
<tr>
<td>3 first or second degree relatives diagnosed &lt;60</td>
<td>2.5-4.0x</td>
</tr>
<tr>
<td>4 first or second degree relatives diagnosed at any age</td>
<td>4.0-5.0x</td>
</tr>
<tr>
<td>Male first degree relative affected at any age</td>
<td>2.5x(female), 6x(male)</td>
</tr>
</tbody>
</table>
Genetics of breast cancer

- Twin study demonstrate 20-30% of breast cancer are caused by heritable factors
- BRCA1 and BRCA2 mutation accounts for 3-8% of all breast cancer cases
- Gene sequencing detects: deletion, substitution, frameshift
- Genomic re-arrangement within BRCA gene which are not detected by gene sequencing
- BRCA1 mutation: 60% lifetime risk of BC; 54% risk of CA ovary
- BRCA2 mutation: 45% lifetime risk of BC; 11% risk of CA ovary
- Polygenic contribution
- Unidentified high penetrance gene
- High frequency, low penetrance breast cancer gene: TGFBR1*6A result in 5% of breast cancer (Type 1 Transforming growth factor β Receptor)

Familial breast cancer syndrome

<table>
<thead>
<tr>
<th>Gene implicated (location)</th>
<th>Syndrome and its features</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53 (chromosome 17p)</td>
<td>Li-Fraumeni syndrome. Early onset breast cancer in females plus (both sexes)</td>
</tr>
<tr>
<td>PTEN (chromosome 10q)</td>
<td>Cowden's syndrome. Skin hamartomas, breast cancer, bowel polyps</td>
</tr>
<tr>
<td>BRCA1 (chromosome 17q)</td>
<td>Early onset breast cancer, substantial risk of ovarian cancer</td>
</tr>
<tr>
<td>BRCA2 (chromosome 13q)</td>
<td>Early onset breast cancer, including risk in males. Risk of ovarian cancer but lower than for BRCA1. Excess of endometrial, bowel, bladder, renal, laryngeal, pancreatic cancers</td>
</tr>
<tr>
<td></td>
<td>Probably increase risk of lymphomas and melanomas</td>
</tr>
</tbody>
</table>

Founder mutations

- Specific mutation in BRCA1 (Ashkenazi Jews) – 195 del AG
- BRCA2 (Icelander) 999 del 5
- BRCA2 – 6174 del T
- Founder mutations in BRCA1 and BRCA2 also identified in Southern Chinese
- Founder mutation facilitate screening testing for the target mutation

Hong Kong Hereditary and High Risk breast cancer program

- 555 high risk tested 2007 to 2011
- 69 mutations (12.4%)
- 29 in BRCA1, 40 in BRCA2
- 29 novel mutation, 12 in BRCA1 and 17 in BRCA2
- 4 are LGR (large genomic rearrangement) detected by MLPA (multiplex ligation dependant probe amplification) only
- 1 BRCA1 mutation and 3 BRCA2 mutation are putative founder mutation in Southern Chinese
BRCA1 and BRCA2 breast cancer

- Young patient
- Family history
- High grade tumour
- ER negative tumour
- Triple negative tumour

Features of BRCA1 and BRCA2 associated tumours

<table>
<thead>
<tr>
<th>Age of onset</th>
<th>About 50% under age 50 (compared with 20% of sporadic cases) but can present at any age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of second primary (breast)</td>
<td>4-6% per year</td>
</tr>
<tr>
<td>Oestrogen receptor status</td>
<td>Majority negative, regardless of age at diagnosis</td>
</tr>
<tr>
<td>Pathological type</td>
<td>Almost always invasive ductal (no special type)</td>
</tr>
<tr>
<td>Pathological grade</td>
<td>Tend to high, with high mitotic index.</td>
</tr>
</tbody>
</table>

Genetic testing

- Feasible
- High cost
- Implication of subsequent treatment
- Impact of insurance policy
- Identified mutation in breast cancer patients
- Offer testing to the family members
- Mutation positive women may consider bilateral oophorectomy and/or risk reduction mastectomy
Genetic testing in young women with breast cancer: results from a Web-based survey

K. J. Ruddy¹, S. Gelber¹, J. Shin², J. E. Garber¹, R. Rosenberg³, M. Przypysny³ & A. H. Partridge¹

- Harvard Medical School, Boston
- 701 women with BC diagnosed <40
- Mean age of diagnosis: 32.9yr
- 41% reported 1st or 2nd relative with breast or ovarian cancer
- 24% had genetic testing
- 26% had mutation demonstrated

Variation in rates of uptake of preventive options by Canadian women carrying the BRCA1 or BRCA2 mutation

- 672 with confirmed mutation
- 342/672 without breast cancer
- A mean of 4 yrs after the diagnosis of genetic mutation
- 72/342 (21%) had prophylactic bilateral mastectomy
- 363/672 (54%) had bilateral prophylactic oophorectomy
- 17/270 (6%) takes tamoxifen
- 157/342 (46%) has not done any preventive measures

Characteristics of bilateral prophylactic mastectomy cohort (n=214)

<table>
<thead>
<tr>
<th>Type of Mastectomy</th>
<th>Deleterious (n=18)</th>
<th>Uncertain (n=8)</th>
<th>No mutation (n=150)</th>
<th>Not tested (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age of prophylactic mastectomy</td>
<td>36.5</td>
<td>44</td>
<td>43</td>
<td>38.5</td>
</tr>
<tr>
<td>Median yrs of followup</td>
<td>13.1</td>
<td>14.7</td>
<td>12.8</td>
<td>13.7</td>
</tr>
<tr>
<td>No of breast/ovarian ca in family</td>
<td>1-3</td>
<td>4</td>
<td>75</td>
<td>19</td>
</tr>
<tr>
<td>&gt;4</td>
<td>17</td>
<td>4</td>
<td>75</td>
<td>19</td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Mean age of dx of breast cancer</td>
<td>41.1</td>
<td>49.8</td>
<td>51</td>
<td>49</td>
</tr>
</tbody>
</table>
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Surgical Options
- Surgery
- Chemotherapy
- Radiotherapy

Breast cancer and pregnancy

- Breast Cancer dx during or within 1 yr after delivery
- Estimated incidence 0.2 to 3.8%
- 1: 3000 to 1: 10 000 pregnancy
- Delayed child bearing age
- Increasing breast cancer incidence in 30 and 40s
- Pregnancy has protective effect against breast cancer
- hCG has protective effect on mammary carcinogenesis in animal model
- Prolactin promote tumour induction and growth in animal model

Diagnosis of Breast cancer during pregnancy

- Breast size and mass increase
- Vascularity increases
- Difficulty in examination
- Inflammatory tumour may be mistaken as mastitis
- Patients fail to report symptoms to her doctor
- Doctor fails to advise appropriate imaging
- Doctor fails to advise biopsy

Termination of pregnancy

- Chance of cure to the patient
- Treatment will cause significant harm to the fetus
- Abortion does not confer a better prognosis
- Present trend: treat the cancer and allow pregnancy to proceed
- General acceptance of chemotherapy during 3rd trimester
- Withhold chemotherapy 3 wks before delivery to avoid neonatal neutropenia
- Timing of delivery and breast cancer surgery in 3rd trimester
Mastectomy

- Traditional method of treatment for breast cancer
- Modified radical mastectomy vs radical mastectomy
- Local control for breast and axilla
- Radiotherapy is not necessary for most cases
- Deformity

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Surgical Options

- Usually enjoy good health with low operative mortality
- Breast conservation will be desired by patient but results inferior compared with patient >50 when concerning IBTR
- Reconstruction is considered after mastectomy
- When implant considered, need to expect complications in long term
- Autologous abdominal flap may have problem of hernia during future pregnancy

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Surgical Options

- Chemotherapy
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Chemotherapy

- Usually tolerate chemotherapy well as good functional status
- Cardiotoxicity: low
- Renal toxicity: low
- Reactivation of hepatitis
- Neuropenia
- Amenorrhea & premature menopause
- Preservation of fertility and future pregnancy

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Radiotherapy

- Whole breast irradiation after breast conservation
- Chest wall irradiation for locally advanced tumour
- Absolute contraindication: pregnancy

Breast cancer & Hormonal therapy
Molecular classification of breast cancer

- **Luminal A**
  - High ER expression and low proliferation

- **Luminal B**
  - Low ER expression and high proliferation

- **HER**

- **Basal like**
  - Triple negative

**TABLE 1.** Breast Cancer Intrinsic Molecular Subtypes: Clinicopathologic Definition and Recommendations for Treatment According to 2011 St. Gallen Expert Consensus*  

<table>
<thead>
<tr>
<th>Intrinsic Subtype</th>
<th>Clinicopathologic Definition</th>
<th>Clinical Management</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>ER+ and/or PR+ + HER2-</td>
<td>Endocrine therapy alone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>K67 low (&lt;14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal B</td>
<td>ER+ and/or PR+ + HER2-</td>
<td>Endocrine therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>K67 high (≥14%)</td>
<td>Cytotoxic drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asp K67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal B/HER2+</td>
<td>HER2 overexpressed or amplified</td>
<td>Endocrine therapy (metastatic and/or lapatinib)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HER2-specific therapy</td>
<td>Cytotoxic drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(metastatic and/or lapatinib)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>ER+ and/or PR+ + HER2-</td>
<td>Endocrine therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HER2 overexpressed or amplified</td>
<td>Cytotoxic drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HER2-specific therapy</td>
<td>(metastatic and/or lapatinib)</td>
<td></td>
</tr>
<tr>
<td>Triple-negative/basal-like</td>
<td>ER+ and/or PR+ + HER2-</td>
<td>Cytotoxic drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Available retrospective analysis of clinical trial data failed to show that the response to endocrine therapy differs in luminal A vs. luminal B tumors when PAM50 is applied. Cutoffs for predicting increased sensitivity to cytotoxic may differ.

Geyer et al. Molecular classification of Estrogen receptor positive luminal breast cancer
Tamoxifen
- Selective Estrogen Receptor Modulator
- Has been used for >40yrs
- 31% decrease of breast cancer mortality
- Estrogen receptor positive breast cancer
- Early breast cancer: adjuvant
- Locally advanced: adjuvant and neoadjuvant
- Metastatic: palliative
- Elderly patient: primary treatment when operation contraindicated due to poor health

Aromatase inhibitors
- Inhibit the action of aromatase (enzyme that produce estrogen in peripheral tissue)
- Postmenopausal ER+ve breast cancer
- Early stage: adjuvant
- Locally advanced
- Metastatic: palliative
- Decrease local recurrence and system metastasis
- Decrease risk of contralateral cancer

Tamoxifen
- Cost effective
- Minimal side effect
- Beneficial to bone metabolism
- Endometrial proliferation
- Risk of endometrial carcinoma (especially with prolonged use)
- Period of use within 5 yrs

Aromatase Inhibitors
- Expensive
- More side effects (osteoporosis, arthralgia, menopausal symptoms)
- More potent compared with tamoxifen
- Use alone or in combination of tamoxifen
  - 2 years of tamoxifen switch to Al
  - 5 years of tamoxifen followed by Al
  - 5 years of Al
LHRH analogue

- Ovarian suppression
- Premenopausal women
- ER positive breast cancer
- With or without the addition of tamoxifen or aromatase inhibitor
- Benefit equivalent to CMF regime
- Avoid the toxicity of chemotherapy
- Side effect: menopausal symptoms and osteoporosis
- Preservation of fertility after termination of treatment

Hormonal resistance of ER positive breast cancer

- 60% breast cancer are positive for LHRH receptors
- ER/PR and HER negative
- LHRH receptors can act as targeting moiety
- Cytotoxic drug can be conjugated to LHRH analogue to target on the LHRH receptor positive cancer cells

- Estrogen-ER interaction causes subsequent transcription and protein synthesis resulting in tumour proliferation
- Interaction between different pathways (HER, EGF, mTOR)
- Downstream up regulation of regulatory pathways
- Resulting in hormonal resistance
- Reversal of resistance by inhibition of specific target (e.g., lapatinib for HER and everolimus for mTOR)
Oncotype Dx

- ER positive invasive breast cancer
- HER not overexpressed
- T stage: 1 or 2
- Lymph node negative (ITC and micrometastasis is acceptable)
- Hormonal therapy is suitable
- To consider whether there is additional benefit of giving chemotherapy
- Cost of testing vs cost and toxicity of chemotherapy
The Oncotype DX assay consistently changed treatment decisions across 7 independent studies.\(^{5,9}\)

<table>
<thead>
<tr>
<th>Before RS</th>
<th>After RS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT + HT → HT (n=387)</td>
<td>CT + HT → HT (n=318)</td>
</tr>
<tr>
<td>CT → HT (n=308)</td>
<td>CT → HT (n=318)</td>
</tr>
<tr>
<td>CT + HT → CT + HT (n=308)</td>
<td>CT + HT → CT + HT (n=318)</td>
</tr>
</tbody>
</table>

Studies have shown that Recurrence Score results reduce chemotherapy use, spare patients the negative health and quality of life impact of unnecessary chemotherapy, and reduce the costs to society and the healthcare system.\(^{13,9}\)