# 婦女癌症概論

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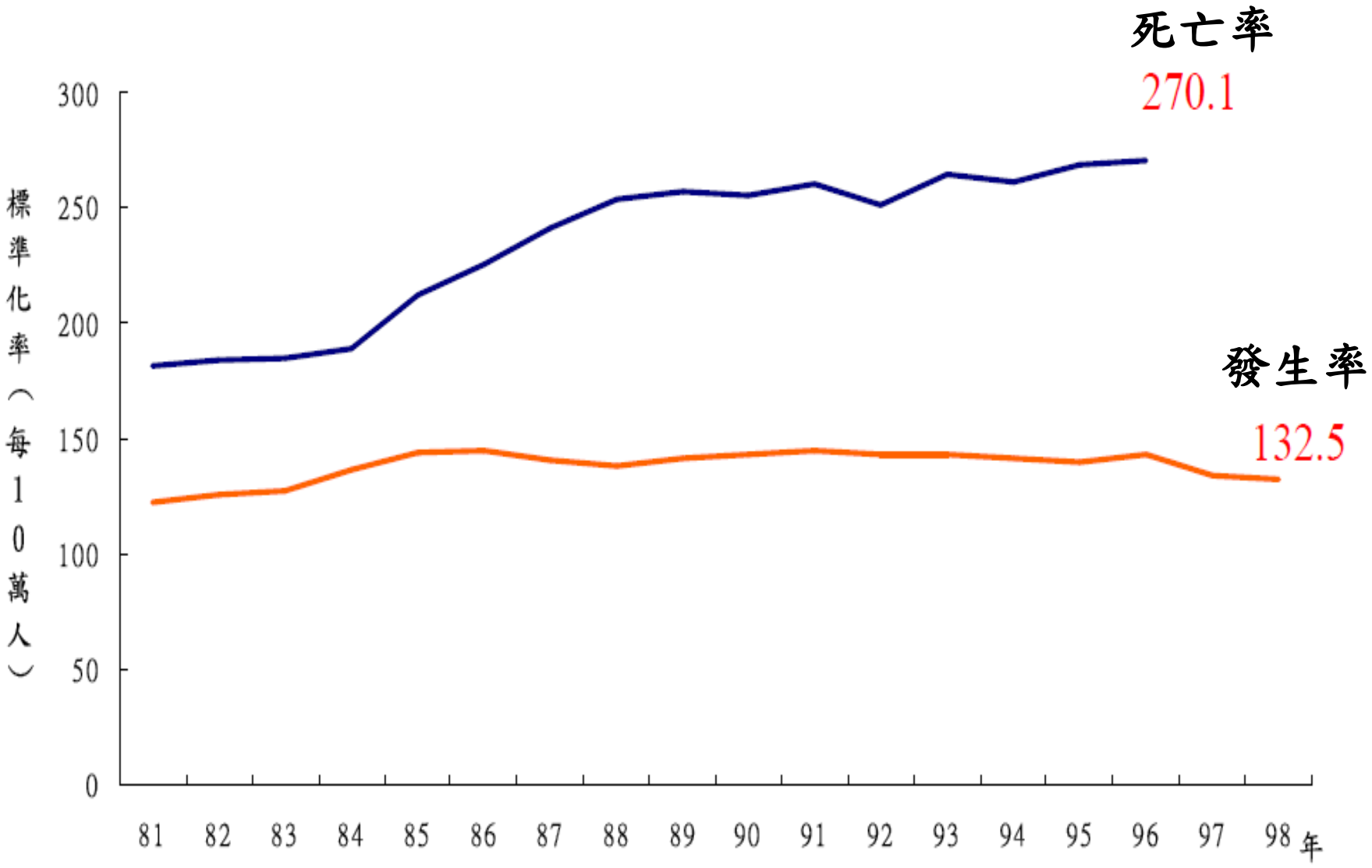
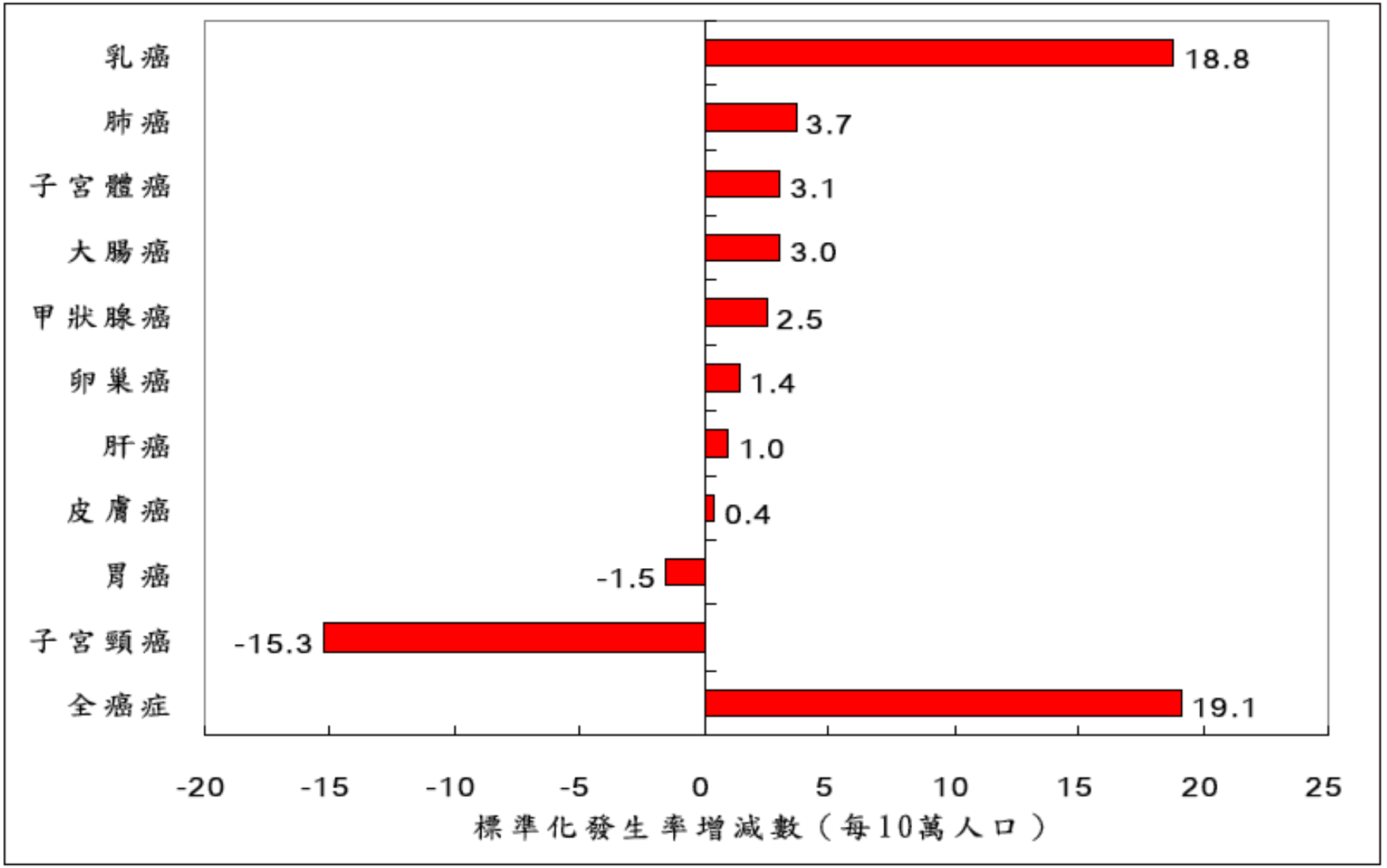
# 台灣婦女癌症現況

(1) 子宮頸癌漸少(子宮頸抹片 早期發現 早期治療 人類乳突病毒疫苗)

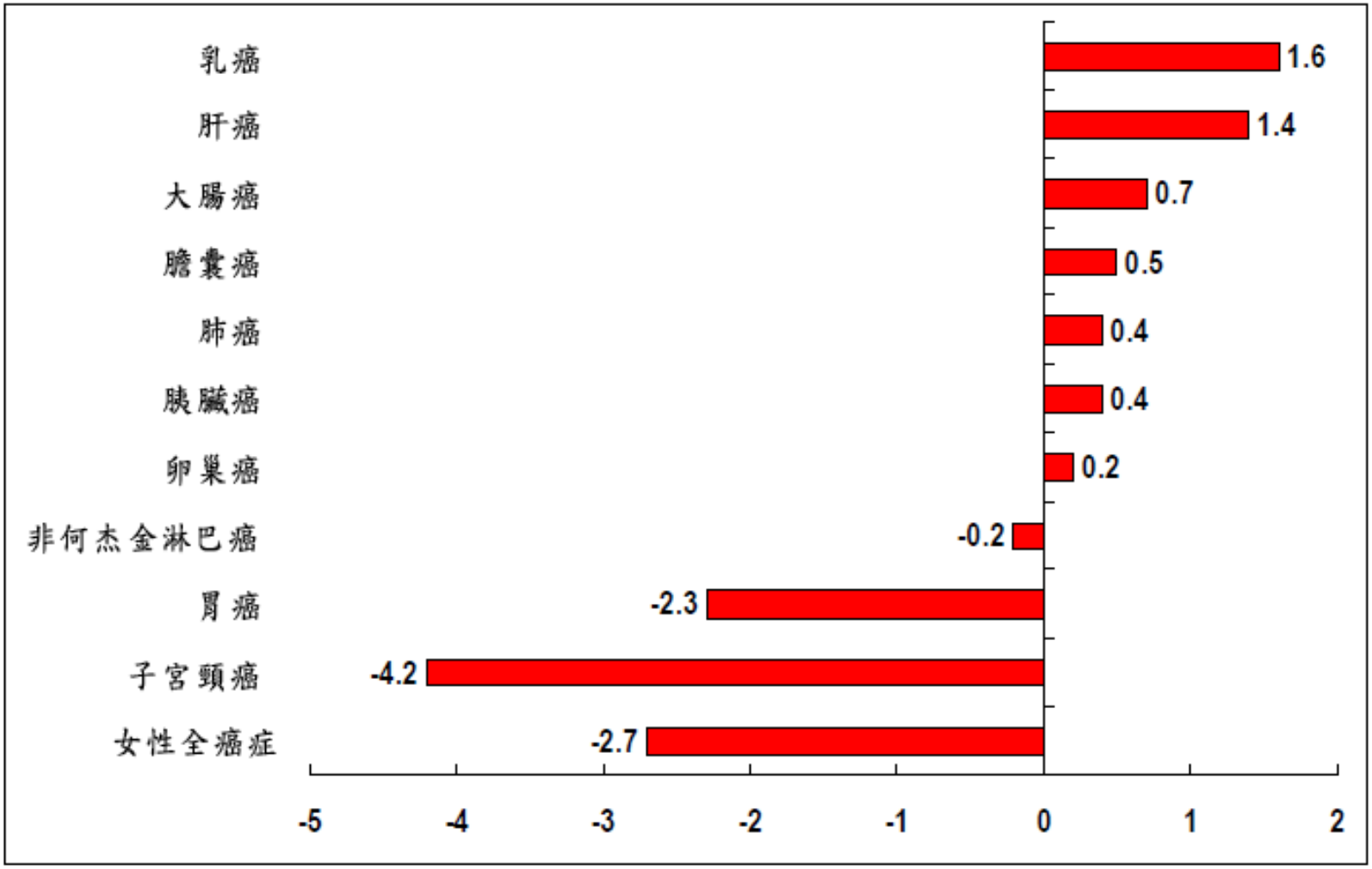
(2) 乳癌子宮內膜癌卵巢癌漸多


死亡率
270.1
發生率
132.5
標準化率（每10萬人）
300
250
200
150
100
50
0
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
年

國健局




女性10大癌症年齡標準化發生率10年增減數,1998~2007




# 女性10大癌症年齡標準化死亡率之10年變化率，1998~2007

# Obesity and GYN cancers

**(1) Obesity greatly increases risk of low grade endometrioid endometrial cancers, with modest increases in risk for high grade cancers.**
**No sufficient data about the association of obesity between recurrence and death.**

**(2) Obesity increases risk of ovary cancer, although may not influence risk of high grade serous cancers that account for the majority of ovary cancer deaths.**
**Obesity associated with reduced survival.**

*ASCO Education Book 2013*

# Obesity and GYN cancers

**(3) Mechanisms:**

***Adipose tissue in postmenopausal women:**
**the source of endogenous estrogen**

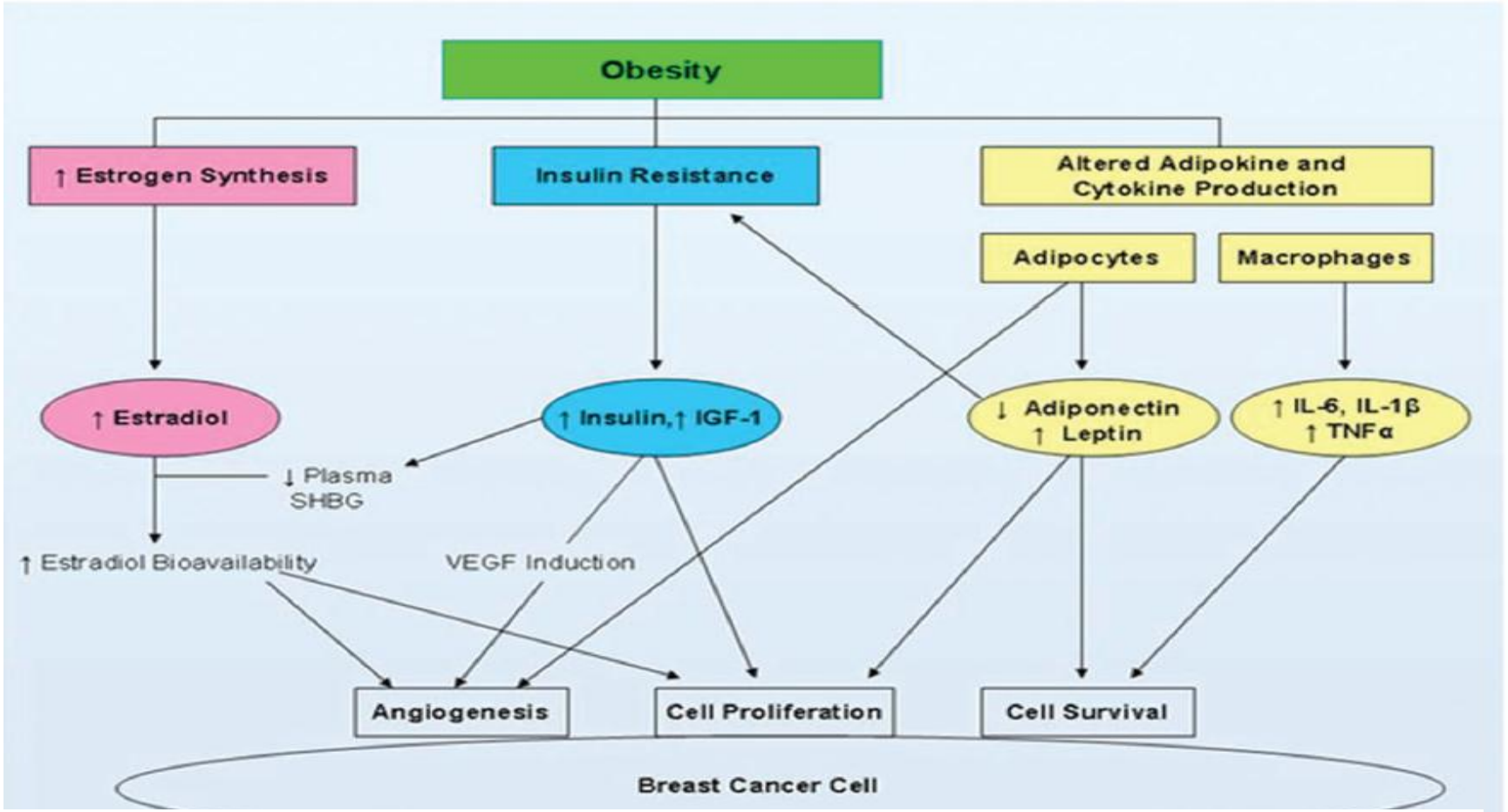
***High estrogen level in obesity without progesterone leads to uncontrolled proliferation of endometrial hyperplasia**
**Related to endometrioid endometrial cancers, some of high grade endometrial cancers, and ovarian cancers.**

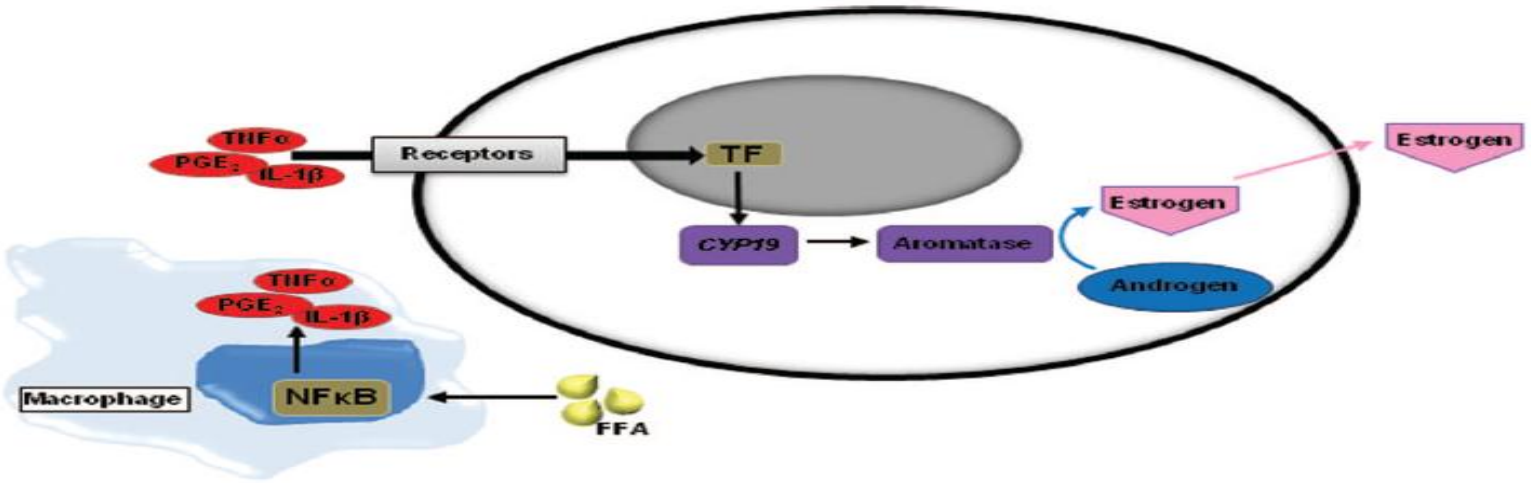
***Adipose tissue produces leptin(growth factor for breast /endometrium and promotes angiogenesis), adiponectin, and IL-6/8.**

***Insulin resistance: cancer risk and adverse outcome**

***More aggressive cancer behavior?**

***More comorbidities in obesity**
**Easy inadequate chemotherapy dosage**


Obesity
↑ Estrogen Synthesis
Insulin Resistance
Altered Adipokine and Cytokine Production
Adipocytes
Macrophages
↑ Estradiol
↑ Insulin, ↑ IGF-1
↓ Adiponectin
↑ Leptin
↑ IL-6, IL-1β
↑ TNFα
↓ Plasma SHBG
↑ Estradiol Bioavailability
VEGF Induction
Angiogenesis
Cell Proliferation
Cell Survival
Breast Cancer Cell


TNFα
PGE2
IL-1β
Receptors
TF
Estrogen
CYP19
Aromatase
Estrogen
Androgen
TNFα
PGE2
IL-1β
Macrophage
NFκB
FFA

# 台灣婦女癌症和國際的比較

1. **HR(+) young female breast cancer, endometrioid carcinoma of uterus, and ovary cancer< 55 y/o in Taiwan.**

   **(age-adjusted incidences increased from 1979-2007 from cancer registry)**

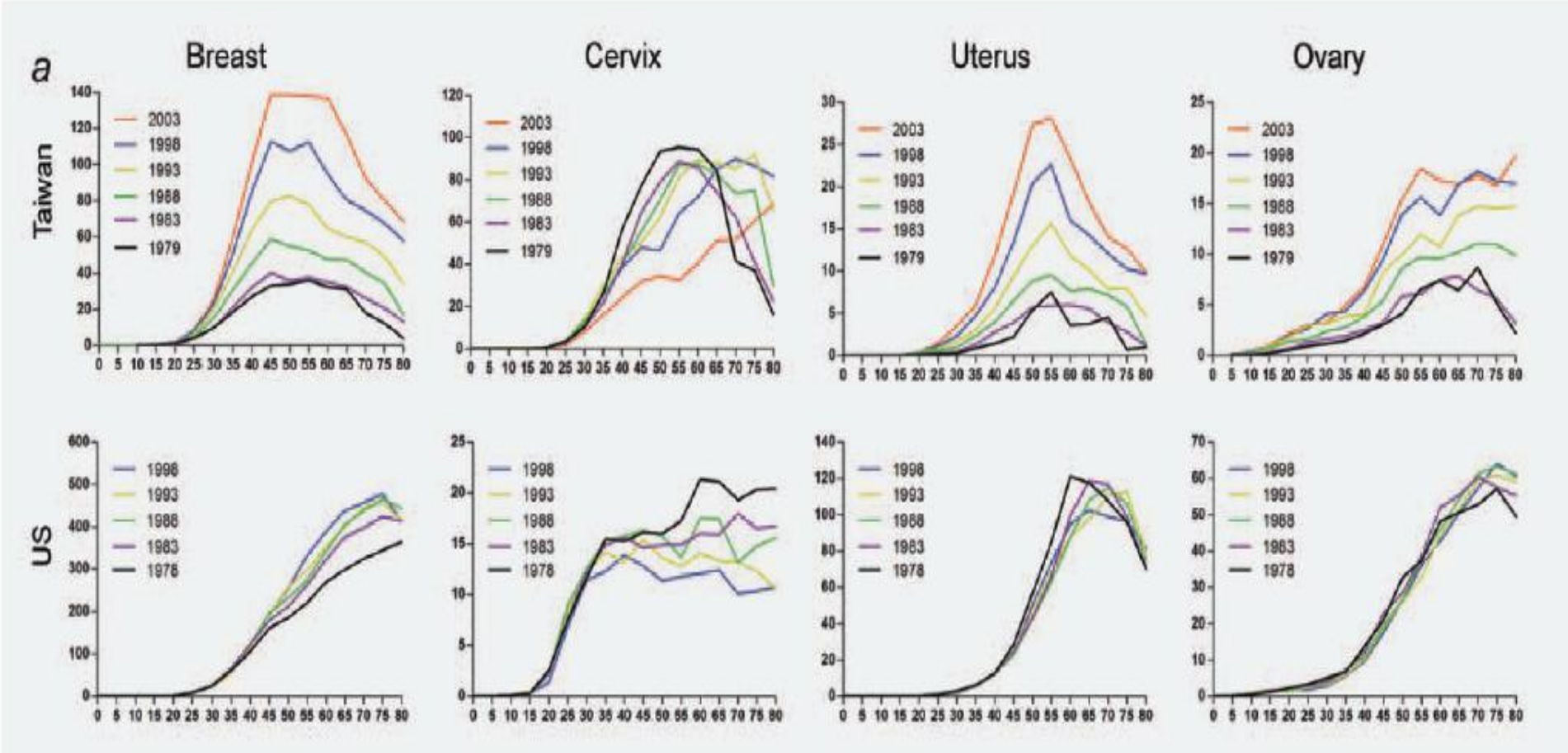
   **Strong estrogen receptor expression in these cancers.**

   **Luminal A type breast cancer predominant .**

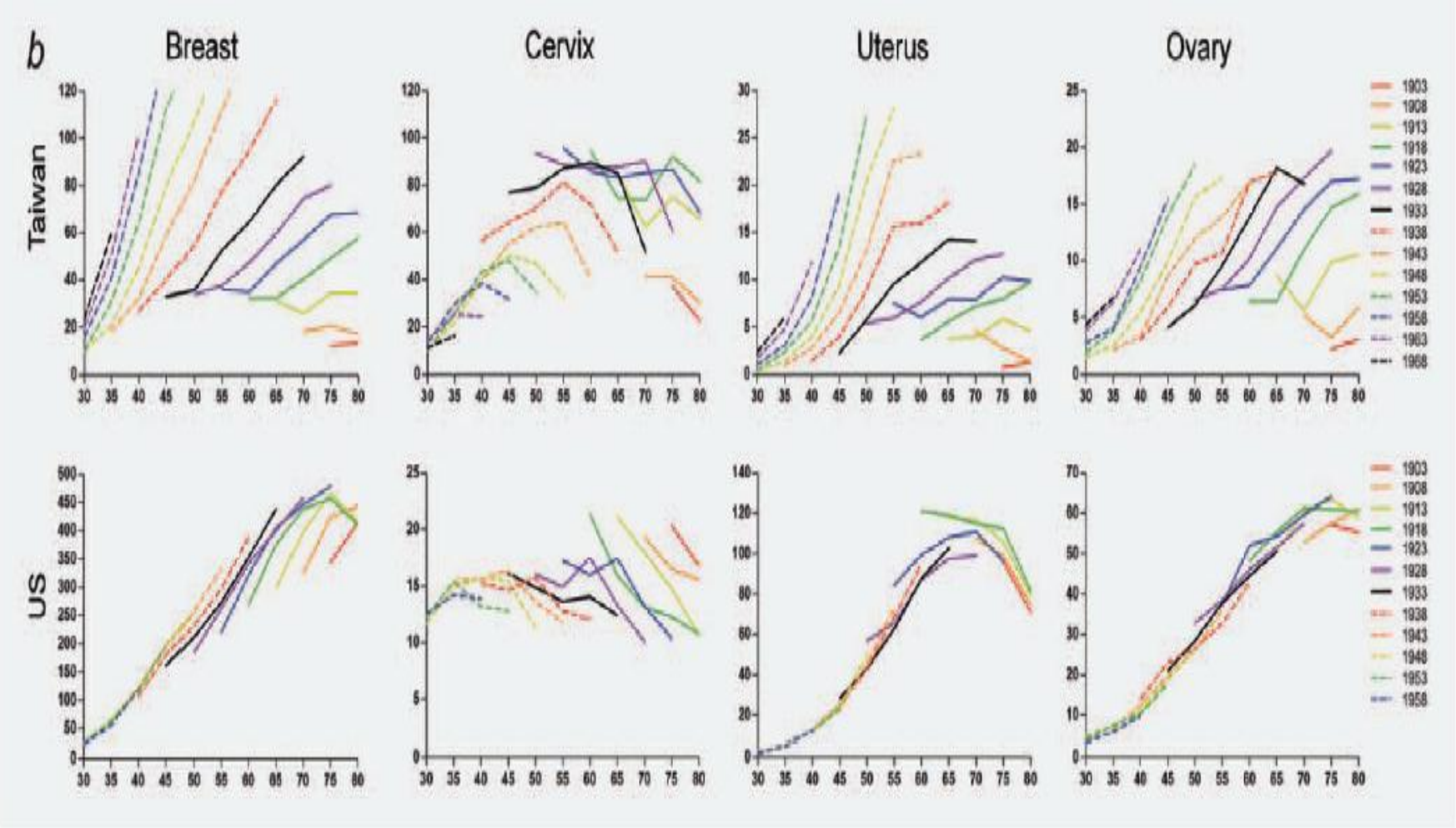
2. **Cervical ca decrease and successful Tx.**

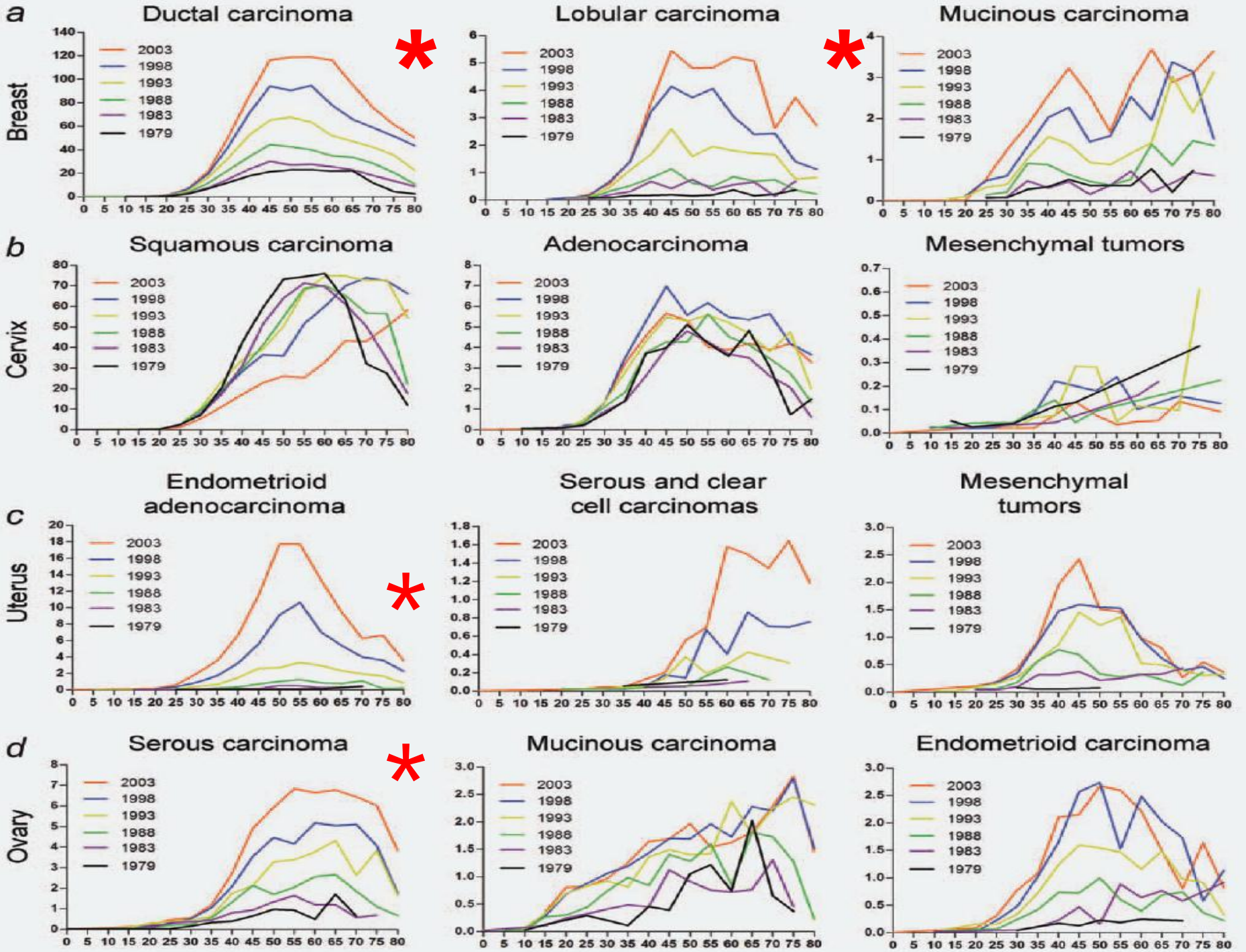
*Ching-Hung Lin, et al. International Journal of Cancer 2012; 130: 2629-2637.*

# By calendar year



# By birth cohort




a
Breast
Ductal carcinoma
Lobular carcinoma
Mucinous carcinoma
b
Cervix
Squamous carcinoma
Adenocarcinoma
Mesenchymal tumors
c
Uterus
Endometrioid adenocarcinoma
Serous and clear cell carcinomas
Mesenchymal tumors
d
Ovary
Serous carcinoma
Mucinous carcinoma
Endometrioid carcinoma
2003
1998
1993
1988
1983
1979

**(1) Bell-shaped curves favoring relatively young age distribution of breast(ductal/lobular carcinoma) and uterine cancers(endometrioid type). ER/PR(+) cancer uniquely frequent in younger P'ts. (different from frequent ER/PR + cancers in older P'ts in western countries)**

**(2) A rapid increase in estrogen-related malignancies in young women in Taiwan.**

| | No. (%) | | No. (%) | | |
|---|---|---|---|---|---|
| | <35 years | 35–50 years | ≤50 years | >50 years | $p^1$ |
| ER+ | 449 (65) | 3,727 (68) | 4,176 (68) | 3,635 (58) | <0.001 |
| ER– | 244 (35) | 1,756 (32) | 2,000 (32) | 2,625 (42) | |
| PR+ | 379 (55) | 3,528 (64) | 3,907 (63) | 3,114 (50) | <0.001 |
| PR– | 314 (45) | 1,955 (36) | 2,269 (37) | 3,146 (50) | |

[1]Comparison between ≤50 and >50 years.

***Young breast cancer patients in Taiwan: (1) High prevalence of Luminal A subtype; (2) Low prevalence of grade 3 and/or basal-like**

***Different from western(esp. African) young breast cancers: triple negative, basal-like, poor-differentiated**

| Population (study period, y) | No. patients | Luminal A (%) | | Luminal B (%) | HER-2+/ER- (%) | Basal-like (%) | Unclassified (%) |
|---|---|---|---|---|---|---|---|
| United States [Carolina Breast Cancer Study (16), 1993-1996] | 496 | | | | | | |
| African American | 196 | | | | | | |
| Premenopausal | 97 | 36 | | 9 | 9 | 39 | 6 |
| Postmenopausal | 99 | 59 | | 16 | 7 | 14 | 4 |
| Non-African American | 300 | | | | | | |
| Premenopausal | 164 | 51 | | 18 | 6 | 16 | 10 |
| Postmenopausal | 136 | 58 | | 16 | 6 | 16 | 4 |
| Korea [1993-1998 (17)] | 776 | 44 | | 8 | 17 | 15 | 16 |
| Japan [2000-2003 (16-18)] | 793 | 63 | | 20 | 7 | 8 | 2 |
| Poland [2000-2003 (19)] | 804 | | | | | | |
| Premenopausal | 217 | 66 | | 5 | 5 | 17 | 6 |
| Postmenopausal | 535 | 68 | | 7 | 9 | 10 | 6 |
| Taiwan (2004-2006) | 1,028 | | | | | | |
| ≤50 y | 515 | 67 | *** | 10 | 10 | 9 | 4 |
| >50 y | 513 | 57 | | 8 | 14 | 17 | 6 |

*Cancer Epidemiology, Biomarkers, & Prevention 2009; 18: 1807-1814.*

# **Possible** mechanisms

**(1) Prolonged reproductive stimulation by endogenous estrogen due to western diet habits and lifestyles in younger females in Taiwan.**
***Not just westernization; because disease characteristics should be similar to those in western countries.***

**(2) Environmental pollutants with estrogenic effects(water, air, and plastic bags for hot foods).**

**(3) Genetic polymorphism of estrogen synthesis and metablism.**

# 乳癌子宮頸癌子宮內膜癌卵巢癌診斷治療新面向

# Local therapy in BC

**(1) NSABP B-32: SLND vs ALND in clinically LN(-) BC--- no difference with fewer complications**

**(2) EORTC AMAROS trial: Radiotherapy vs ALND: similar control with fewer complications in SLND(+) BC**

*ASCO Proceedings 2013*

# Adjuvant chemotherapy in BC

**(1) Low to intermediate risk in elderly luminal A BC and low risk in young luminal A BC could avoid adjuvant chemotherapy.**

**(2) Integrating molecular and genomic signatures to determine the use of chemotherapy and targeted therapy in this era.**

**(3) S0221: FEC combined with weekly paclitaxel has better therapeutic profiles vs FEC with triweekly or dose-dense paclitaxel.**

**(4) GEICAM2003-10 trial: EC followed by docetaxel(EC-T) vs epirubicin, docetaxel, & capecitabine(ET-X) has better DFS.**

*ASCO Educational Book 2013*

# Neo-Adjuvant chemotherapy in BC

**(1)An opportunity to obtain insights to tumor biology, evaluate new agents(C/T, hormone Tx, & targeted Tx), improve pCR rates, identify predictive biomarkers, and tailoring surgical extent/ chemotherapy regimens/ radiation dosage.**

**(2)GeparSixto trial: Adding carboplatin to neoadjuvant paclitaxel and doxorubicin enhances clinical benefits in triple negative BC.**

**(3)PrECOG 0105 study: Gemcitabine and carboplatin with iniparib effective in neoadjuvant settings for triple negative and BRCA1/2 mutation BC**

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# Adjuvant Tamoxifen in BC

**aTTOM: Prolonging adjuvant tamoxifen to 10 years vs stopping at 5 years still have benefits to reduce recurrence and increase survival, esp. in relatively young pre-menopausal women.**

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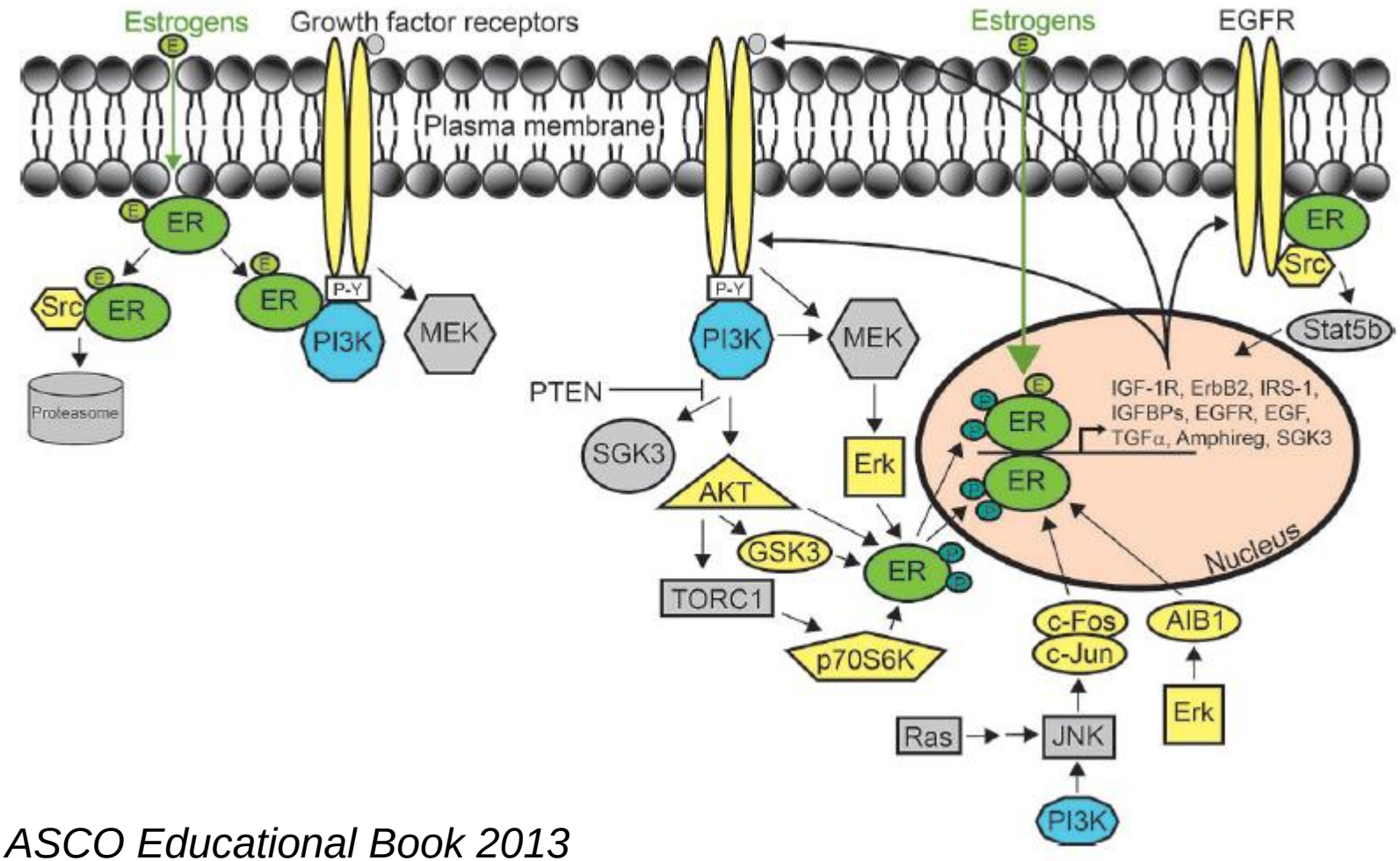
# Endocrine resistance in BC

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| | Kaufman 2009[26] | | Johnston 2009[27] | | Cristofanilli 2010[29] | | Osborne 2011[30] | | Baselga 2012[31] | | Finn 2012[34] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ana | Ana + Tras | Let + Placebo | Let + Lapatinib | Ana + Placebo | Ana + Gefitinib | Tam + Placebo | Tam + Gefitinib | Exe + Placebo | Exe + Everolimus | Let | Let + PD0332991 |
| n | 104 | 103 | 108 | 111 | 50 | 43 | 101 Stratum 1 | 105 Stratum 1 | 239 | 485 | 81 | 84 |
| CBR | 27.9% | 42.7% | 29% | 48% | 34% | 49% | 45.5% | 50.5% | NR | NR | 44% | 68% |
| PFS (months) | 3.8 | 5.6* | 3.0 | 8.2* | 8.4 | 14.7* | 8.8 | 10.9* | 2.8 | 6.9* | 7.5 | 26.2* |
| OS (months) | 23.9 | 28.5 | NR | | NR | | NR | | NR | | NR | |
| Significance* | hazard ratio = 0.63 95% CI: 0.47-0.84 | | hazard ratio = 0.71 95% CI: 0.53-0.96 | | hazard ratio = 0.55 95% CI: 0.32-0.94 | | hazard ratio = 0.84 95% CI: 0.59-1.18 | | hazard ratio = 0.43 95% CI: 0.35-0.54 | | hazard ratio = 0.32 95% CI: 0.19-0.56 | |
| Target | HER2 | | HER2 | | EGFR | | EGFR | | mTOR | | CDK 4/6 | |

Abbreviations: Ana, anastrozole; CBR, clinical benefit rate; EGFR, epidermal growth factor receptor; Exe, exemestane; Ful, fulvestrant; HR+, hormone-receptor positive; Let, letrozole; Meg, megestrol; MBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; NR, not reported; PFS, progression-free survival; Tras, trastuzumab.

| Target | Agent | Stage and Study Number | Estimated Enrollment (n pts) |
|---|---|---|---|
| PI3K/AKT/mTOR | XL147 (inhibitor of PI3K) or XL765 (dual inhibitor of PI3K and mTOR) plus letrozole | Phase I/II (NCT01082068) | 99 |
| *** | GDC-0941 + fulvestrant or GDC-0980 + fulvestrant or placebo + fulvestrant | Phase II (NCT01437566) | 270 |
| | BKM120 (pan-PI3K inhibitor) plus fulvestrant vs. placebo plus fulvestrant | Phase III (NCT01633060) | 615 |
| | MK-2206 (Akt inhibitor) plus anastrozole, or letrozole, or exemestane, or fulvestrant | Phase I (NCT01344031) | 54 |
| Histone deacetylase (HDAC) | entinostat (SNDX-275) plus exemestane versus placebo plus exemestane | Phase II (NCT00676663) | 125 |
| Vascular endothelial growth factor/angiogenesis | Bevacizumab plus tamoxifen or letrozole vs. tamoxifen or letrozole alone | Phase III (NCT00601900) | 502 |
| | Bevacizumab plus letrozole or fulvestrant vs. letrozole or fulvestrant alone | Phase III (NCT00545077) | 378 |
| | BMS-690514 (inhibitor of EGFR, HER2, and VEGF receptor kinases) plus letrozole versus lapatinib plus letrozole | Phase II (NCT01068704) | 140 |
| Proteasome (NF-kB pathway) | Bortezomib plus fulvestrant vs. fulvestrant alone | Phase II (NCT01142401) | 118 |
| Src kinase | Dasatinib plus fulvestrant vs. fulvestrant alone | Phase II (NCT00754325) | 100 |
| | Dasatinib plus exemestane vs. exemestane alone | Phase II (NCT00767520) | 157 |
| Fibroblast growth factor receptor (FGFR) | AZD4547 plus fulvestrant vs. fulvestrant alone | Phase I/II (NCT01202591) | 120 |
| Insulin-like growth factor type 1 (IGF-1) | MEDI-573 (Dual IGF-I/II-neutralizing antibody) plus AI vs. AI Alone | Phase Ib/II (NCT01446159) | 193 |
| | BMS-754807 plus letrozole vs. BMS-754807 alone | Phase II (NCT01225172) | 59 |
| | MM-121 plus exemestane vs. exemestane alone | Phase II (NCT01151046) | 130 |
| Cyclin dependent kinase (CDK) 4/6 | PD-0332991 plus letrozole vs. letrozole alone | Phase I/II (NCT00721409) | 177 |
| | PD-0332991 plus letrozole vs. placebo plus letrozole | Phase III (NCT01740427) | 450 |

# HER2(+) BC

**(1)BOLERO-3: Everolimus(mTORi) increases PFS although modest when adding to vinorelbine and trastuzumab in trastuzumab-resistant advanced BC.**

**(2)CLEOPATRA study: Pertuzumab increases PFS when adding to docetaxel with trastuzumab in the 1st line MBC.**

**(3)EMILIA trial: MBC previously treated with docetaxel and trastuzumb--- T-DM1 vs capecitabine and lapatinib: superior PFS in T-DM1**

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| Class of Compounds | Agent(s) | Mechanism of Action |
|---|---|---|
| Monoclonal antibody | Trastuzumab | • Inhibition of ligand-independent HER2/3 dimerization<br>• Inhibition of HER2-mediated intracellular signaling<br>• Induction of ADCC |
| | Pertuzumab | • Inhibition of ligand-dependent HER2/3 dimerization<br>• Inhibition of HER2-mediated intracellular signaling<br>• Induction of ADCC |
| Antibody drug conjugates | Trastuzumab-DM1 | • Trastuzumab's action<br>• Selective delivery of the antimicrotubule agent DM1 |
| Small-molecule inhibitors | Lapatinib | • Kinase activity (reversible) inhibition of full-length HER2<br>• Kinase activity (reversible) inhibition of p95HER2 |
| | Afatinib, neratinib | • Kinase activity (irreversible) inhibition of EGFR/HER2/HER4<br>• Kinase activity inhibition of mutated HER2 |

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# Ovarian cancer

**(1)MITO-7 study: Weekly paclitaxel and carboplain(PC) inferior to tri-weekly schedule in efficacy but less toxicity, maybe use in elderly.**

**(2)AGO-OVAR16 study: Pazopanib maintenance after PC offers PFS compared with placebo.**

**(3)NCT00753545(randomized phase 2 trial): PARPi (olaparib) prolongs PFS compared with placebo in platinum-sensitive relapsed serous ovarian cancers, esp. in tumors harboring BRCA mutations.**

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# Molecular pathways in gyn cancers

***PIK3CA mutations and amplifications common in endometrial, ovarian, and cervical cancers.**

***PTEN mutations and deletions frequent in endometrial cancers.**

| | | EC - TYPE | | OC - TYPE* | | CC - TYPE | |
|---|---|---|---|---|---|---|---|
| Target | Alteration | I (%) | II (%) | I (%) | II (%) | SCC (%) | AC (%) |
| ERBB2 | Amplification | 1 | 17 | H | 1 | 14 | 25 |
| FGFR2 | Mutation | 10-16 | 1 | | <1 | | |
| PTEN inactivation | Mutation, deletion, methylation | 50 | 10 | 25 | <1 | 3 | 4 |
| AKT | Mutation | 3 | 0 | 3 | <1 | | |
| | Amplification | | | <1 | 17 | | |
| KRAS | Mutation | 11-26 | 2-4 | 30 | <1 | 3 | 14 |
| | Amplification | 2 | 10 | <1 | 11 | | |
| PIK3CA | Mutation | 30 | 15 | 40 | <1 | 13 | 10 |
| | Amplification | 2-14 | 46 | <1 | 17 | 60 | 80 |
| PIK3R1 | Mutation | 43 | 12 | | | | |

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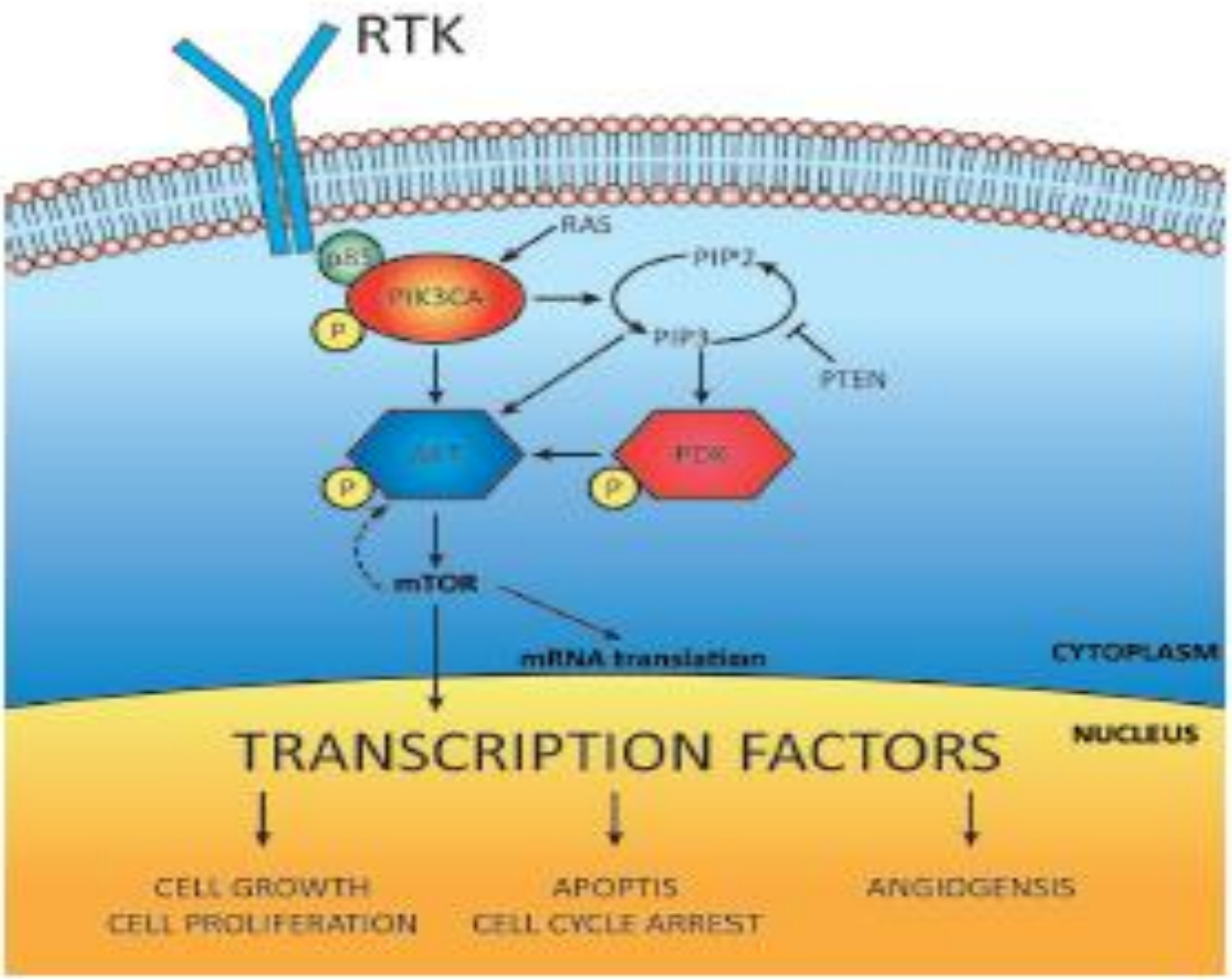
RTK
RAS
PIK3CA
P
PIP2
PIP3
PTEN
P
P
mTOR
mRNA translation
CYTOPLASM
NUCLEUS
TRANSCRIPTION FACTORS
CELL GROWTH
CELL PROLIFERATION
APOPTIS
CELL CYCLE ARREST
ANGIOGENSIS

# Bevacizumab increases suvival in cervical cancer

**(1) Bevacizumab with chemotherapy vs chemotherapy:**
**OS benefit(+)**

**(2) The 1st drug to increase OS in cervical cancers**

**(3) VEGF interventions in cervical cancers launching**

*ASCO proceedings 2013*

# Rare epithelial ovarian cancers

**(1)Mucinous and clear cell ovarian cancers:**
- ***easy early-staged; may not need adjuvant chemotherapy**
- ***advanced stage: carboplatin-resistant**

**(2)Mucinous biology similar to CRC**
- ***May benefit from 5-FU and oxaliplatin**
- ***May have wild K-ras and HER2 amplification— may benefit from cetuximab and trastuzumab**

**(3)Clear cell: might benefit from anti-angiogenesis Tx**

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# Low grade serous ovarian cancers

**(1)MAPK pathway prominent; K-ras mutation 20-40% (MEKi value)**
**Low frequency of p53 mutation**
**Greater expression of ER/PR(anti-hormone Tx)**
**Greater expression of PAX2 and IGF-1**

**(2)Relatively young age, relatively chemoresistance, and prolonged OS.**

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# 篩檢及預防

(1) 乳房攝影
Chemoprevention

(2) 子宮頸抹片
HPV vaccines

# Cancer prevention

**Avoid carcinogens exposure*

**Lifestyle modification*

**Chemoprevention*

**Surgical prevention*

**Vaccination*

**A to K of factors associated with specific cancer sites: an empirical basis for recommending lifestyle changes**

Alcohol consumption > 3 units a day: most squamous cancers, especially bladder and oesophagus

Body mass index > 25 and certainly > 30: all solid cancers

Cigarette smoking at any level (even passive smoking): bladder, lung, head and neck, oesophagus, and oropharyngeal cancers

Diet, especially one that is high in fat: all solid cancers

Exercising < 30 minutes a day: all solid cancers

Family history of cancer (in at least one first degree relative and at least three people in two or more generations): inherited cancer syndromes, including breast, colorectal, diffuse gastric, ovarian, prostate, and uterine cancers

Genital and sexual health (sexually transmitted infections): cervical cancer

Health promoting drugs that may decrease global cancer risks (but need a careful risk benefit analysis): colonic adenomas can be treated with low dose aspirin but can have serious side effects; hormone replacement therapy is linked with breast cancer

Intense sunburn: melanoma

Job related factors: lung cancer (exposure to asbestos and particulates), skin cancer (contact with arsenic)

Known disease associations: colorectal cancer has predisposing mucosal pathology—adenomas, coeliac disease, ulcerative colitis

*Janusz Jankowski, et al. BMJ 2006; 331: pp618.*

# High Fat

**(1)High fat foods increase premenopausal**

**breast cancer risks.**

(2)Colon cancer.(esp. red meat)

(3)High grade prostate cancer.

# Obesity

Obesity and physical inactivity increase cancer risks.

**CRC**

**Breast cancer**

**Endometrial cancer**

**Esophageal cancer**

# 子宮頸癌篩檢

有關上開各類癌症篩檢之對象及篩檢間隔，各國目前採行不同標準。在子宮頸癌篩檢部分，美國防癌協會（ACS）建議，婦女開始有性行為三年內，應開始每年接受抹片檢查，30 歲以上婦女，如連續三年抹片正常者，改為二至三年一次，如合併 HPV 及抹片檢查，HPV 陰性且抹片正常者，改為每三年一次。國際癌症研究組織（IARC）則建議 25 歲以上婦女，每三至五年接受一次抹片檢查即可有效降低子宮頸癌的發生率和死亡率。

1995~2009年婦女子宮頸癌年齡標準化死亡率已呈下降趨勢，由1995年每十萬人口11人死亡降到2009年每十萬人口有4.2人死亡，標準化死亡率下降62%。子宮頸侵襲癌年齡標準化發生率，在實施全國抹片篩檢後，由1995年每10萬人口25人降至2007年每10萬人口12人，標準化發生率下降52%，顯示長期推動抹片篩檢成效已反映在子宮頸癌發生率及死亡率下降的成果上。

# HPV vaccines

| Study | Koutsky et al. [19] (Merck study) | Harper et al. [21] (GlaxoSmithKline study) |
|---|---|---|
| **Design** | Randomized double-blind controlled trial | Randomized double-blind controlled trial |
| **Age (years)** | 16–25 | 15–25 |
| **No. of enrollees** | 2,392 | 1,113 |
| **Location** | 16 sites in the U.S. | 32 sites in North America and Brazil |
| **Antigen** | 40 µg HPV-16 L1 VLP | 20 µg HPV-16 L1 VLP<br>20 µg HPV-18 L1 VLP |
| **Adjuvant** | 225 µg aluminum hydroxyphosphate sulfate | 500 µg aluminum hydroxide and 50 µg 3-deacylated monophosphoryl lipid (ASO4) |
| **Vaccination schedule** | 0, 2, and 6 months | 0, 1, and 6 months |
| **Follow-up** | Mean of 17.4 months | Up to 27 months |
| **Specific titers compared with natural infection** | 60 times greater | 50 times greater for HPV-16;<br>80 times greater for HPV-18 |
| **Clinical outcome** | 100% efficacy preventing persistent HPV-16 infection.<br>No cytologic or histologic abnormalities. | 100% efficacy preventing persistent HPV-16/18 infection.<br>93% efficacy preventing cytological abnormalities. |
| **Adverse effects** | Nonsignificant | Nonsignificant |

*Ali Mahdavi. et al. Oncologists 2005; 10: pp528-538.*

# HPV vaccines

| Study | Garcia et al. [43] ZYC101 | Einstein et al. [41] hspE7 |
|---|---|---|
| Design | Randomized double-blind controlled trial | Single-stage phase II design |
| Age (years) | 18 or older | Not specified |
| No. of enrollees | 127 | 31 |
| Delivery system | Encapsulated polynucleotide | Mycobacterium bovis BCG heat shock protein |
| Antigen | HPV-16 and HPV-18 E6/E7 | HPV-16 E7 |
| Disease group | CIN2/3 | CIN3 |
| Vaccination schedule | 0, 3, and 6 months | 0, 1, and 2 months |
| Follow-up | 6 months | 4 months |
| Clinical outcome | 67%–72% resolution of CIN2/3 in < 25-years-old age group (23% in placebo group) | 48% resolution of CIN3;<br>19% partial response;<br>33% stable disease |
| Adverse effects | Injection site pain, erythema, and induration | Not specified |

*Ali Mahdavi. et al. Oncologists 2005; 10: pp528-538.*

研究證實，子宮頸癌的發生是因感染人類乳突病毒（HPV）所引起。我國分別於 2006 及 2008 年核准「嘉喜」及「保蓓」兩個 HPV 疫苗廠牌上市，可以有效預防 HPV；由於疫苗昂貴且長期效果未確定，社會對於是否以公費補助接種，仍存疑慮。衛生署為讓社會大眾認識 HPV 與子宮頸癌關係，及研議 HPV 疫苗政策，除辦理法人論壇及專業人員教育、完成政策評估報告，提供低收入戶和山地離島青少女免費接種，更於 2008-2009 年進行下列工作：

（一）進行 HPV 疫苗與子宮頸癌防治的民眾宣導教育：

1. 辦理民眾宣導教育

（1）利用電視、報章、雜誌、廣播等大眾傳播媒體，宣導子宮頸癌防治及認識 HPV 疫苗。

（2）於健康 99 衛生教育資訊網設立 HPV 疫苗主題館，提供相關訊息。

（3）利用衛生局所管道，分送民眾「女人的私密筆記」手冊，及「遠離 HPV 魔法書」手冊，介紹子宮頸癌與 HPV 關係、認識 HPV 疫苗及如何預防子宮頸癌。

（4）補助民間單位辦理子宮頸癌防治宣導及成立網路部落格。

2.配合性教育管道，將子宮頸癌防治及疫苗教育納入

（1）製作「螢火蟲之戀」教學光碟及「子宮頸癌防治：性事知多少」教學簡報檔，結合健康促進學校及各縣市衛生局相關管道，於性教育宣導時配合使用。

3.辦理專業人員教育訓練

# 乳癌篩檢

在乳癌篩檢部分，美國防癌協會（ACS）建議，40 歲以上婦女應每年一次接受乳房攝影檢查及專科醫師觸診，20 至 39 歲婦女每三年接受一次專科醫師觸診。惟歐洲國家研究建議為 50 歲以上婦女每二至三年一次乳房攝影檢查，可以降低 35%乳癌死亡率，但認為 40-49 歲篩檢效果仍存爭議。

乳癌位居我國女性癌症發生率第一位及死亡率第四位。根據癌症登記統計顯示，乳癌發生人數從 1995 年 2,838 人增加至 2007 年 7,502 人，標準化發生率上升 93%。而死亡人數也從 1995 年,918 人增加至 2009 年 1,588 人，標準化死亡率上升 9.3%。對於乳癌篩檢，歐美至今已有多項以乳房攝影作為篩檢工具的大型臨床隨機研究,顯示每 1~2 年一次的乳房攝影，可

降低 50~69 歲婦女乳癌死亡率 21-34%。

# High risk for familial BC

NCCN® Practice Guidelines in Oncology – v.1.2006

## Hereditary Breast and/or Ovarian Cancer

Guidelines Index
Genetics Table of Contents
MS, References

**HBOC CRITERIA[a,b]**

- **Member of family with a known BRCA1/BRCA2 mutation**

- **Personal history of breast cancer + one or more of the following:**
  - **Diagnosed age ≤ 40 y,[c] with or without family history**
  - **Diagnosed age ≤ 50 y[c] or two breast primaries,[d] with ≥ 1 close blood relative with breast cancer ≤ 50 y or ≥1 close blood relative with ovarian cancer**
  - **Diagnosed at any age, with ≥ 2 close blood relatives with ovarian cancer at any age**
  - **Diagnosed at any age with ≥ 2 close blood relatives with breast cancer, especially if ≥ 1 woman is diagnosed before age 50 y or has two breast primaries[d]**
  - **Close male blood relative with breast cancer**
  - **Personal history of ovarian cancer**
  - **If of certain ethnic descent associated with deleterious mutations (eg, founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other) or history of breast and/or ovarian cancer in close blood relative; no additional family history required**

- **Personal history of ovarian cancer + one or more of the following:**
  - **≥ 1 close blood relative with ovarian cancer**
  - **≥ 1 close female blood relative with breast cancer at age ≤ 50 y or two breast primary cancers[d]**
  - **≥ 2 close blood relatives with breast cancer**
  - **≥ 1 close male blood relative with breast cancer**
  - **If of Ashkenazi Jewish descent, no additional family history is required**

- **Personal history of male breast cancer particularly if one or more of the following is also present:[e]**
  - **≥ 1 close male blood relative with breast cancer**
  - **≥ 1 close female blood relative with breast or ovarian cancer**
  - **If of certain ethnic descent associated with deleterious mutations (eg, founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other), no additional family history is required**

- **Family history only—Close family member meeting any of the above criteria**

**Criteria met** → Follow-up (see HBOC-2)

**Criteria not met** → Refer to NCCN Breast Cancer Screening and Diagnosis Guidelines

[a]One or more of these criteria is suggestive of hereditary breast/ovarian cancer syndrome that warrants further professional evaluation.

[b]When investigating family histories for HBOC, all close relatives on the same side of the family should be included. Close relatives include first-, second-, and third-degree relatives. Other malignancies reported in some families with HBOC include prostate, pancreatic, and melanoma. The presence of these cancers may increase suspicion of HBOC.

[c]May consider age range between ≤ 40 and ≤ 50 y if clinical situation warrants.

[d]Two breast primaries including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors.

[e]Males with limited family history may have an underestimated probability of familial mutation.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.**

Back to Assessment (see BR/OV-1)

# High risk for BC

**Gail scores:(mainly for hormone receptor positive)**

**(1) Age**
**(2) Family history of BC**
**(3) Age of the first birth or nulliparity**
**(4) Number of breast biopsies**
**(5) Age of menarche**
**(6) Pathologic diagnosis of atypical hyperplasia**

# Breast Cancer Primary Prevention Trials---Tamoxifen

- NSABP-P1(n=13,388): 69% reduction in ER(+) breast cancer, no effects on ER(-) breast cancer
- The Royal Marsden trial and the Italian Study showed only benefit in high risk group and women with HRT.
- The IBIS trial showed 33% reduction in the incidence of breast cancer.

**For young women with high risk.**

JNCI 1998;90:1371-88

# Breast Cancer Primary Prevention---RAloxifene

- The CORE Study (MORE Trial): 7705 osteoporotic women, raloxifene for 8 years, reduced breast cancer risk by 66% (76% in ER(+), no effects in ER(-))
- No increased risk in endometrial cancer
- Increased risk in VTE(HR: 3.1)

**For elderly, osteoporosis, or tamoxifen contraindications.**

Proc Am Soc Clin Oncol 2004;23:97

# The STAR Trial
# Tamoxifen vs. Raloxifene

- 19,747 postmenopausal women with predicted 5-year breast cancer risk of more than 1.66%
- Randomized to 5 year tamoxifen(20mg) or raloxifene(60mg)
- No difference in invasive carcinoma, fractures, cardiac events, and deaths
- More noninvasive breast cancer in raloxifene (HR: 1.41, 1.00~2.02)
- Less endometrial cancer in raloxifene (HR: 0.62 0.35~1.08)
- Raloxifene had less DVT and PE

JAMA 2006;295:2727-2741

# In Geneticlly High Risk Women

- A case-control study showed a favorable trend toward a reduction of contralateral breast cancer in BRCA1 mutation carriers receiving adjuvant tamoxifen regardless of hormone receptor status.
- In NSABP-P1, tamoxifen reduced breast cancer risk in BRCA2, but not in BRCA1

Lancet 2000;356:1876-1881
JAMA 2001;286:2251-2256

# Surgical prevention

**(1)BRCA1/2: Bilateral mastectomy and bilateral salpingo-oophorectomy**

(2)HNPCC/FAP: total colectomy

**(3)Endometrial ca related to HNPCC: total abdominal hysterectomy and bilateral salpingo-oophorectomy**

(4)Medullary thyroid ca(MENIIA): total thyroidectomy in childhood

# BRCAness

**(1) Early screening with breast echo/mammography / even MRI**

**(2) After childbearing, bilateral salpingo-oophorectomy followed by tamoxifen prevention(monitor endometrial thickness and DVT)**

**(3) If needed, bilateral mastectomy for breast lesions and total abdominal hysterectomy for endometrial lesions.**

# Ovarian cancer risk reduction in high risk patients

*****Metformin use in high risk women: early results only**

*ASCO Educational Book 2013*

# 婦癌團體

本院---女人花：針對所有婦癌患者

期待　增強互助支持
減少焦慮不安
提供正確觀念
交換就醫資訊
加強醫病溝通