Folic Acid / Cervical Cancer

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Cervical Cancer

- Cx Ca one of the most preventable ca in women
- Predominantly attributed to HPV infection
- In less-developed countries
  - Cx Ca incidence has increased
  - 2nd most-commonly ca/ 3rd leading cause of ca death in women
- In developed countries:
  - high screening rates and significant reductions in cx ca mortality
- The main risk factor
  - Oncogenic HPV infection, preceded by preca changes of the cx (CIN)

Additional risk factors for CIN/ Cx Ca

- Socioeconomic status
  - Nutrient, including FA supplement
- Race
- smoking
- younger age at first intercourse,
- high parity,
- oral contraceptive use

Folic Acid Deficiency

- Folate deficiency and ca development
- Growing evidence:
  - nutrients, particularly folate are in the process of cx carcinogenesis
    - via DNA methylation and synthesis
- Some studies suggested:
  - folate intake/supplement, levels of folate, play a role in cx carcinogenesis

Beneficial effects of folate…

- Possible mechanisms (1)
  - Folate is the cofactor for methionine synthase
    - which catalyzes the conversion of homocysteine
    - folate levels are therefore inversely associated with homocysteine levels
    - Hyperhomocysteinemia
      - associated with higher risks of some birth/preg outcomes, ca, CVD, neurological conditions

Beneficial effects of folate…

- Possible mechanisms (2)
  - Polymorphisms of 5,10- methylenetetrahydrofolate reductase
  - Are critical junctions in the folate-metabolizing pathway
    - guiding folate metabolites to the DNA methylation pathway
    - away from the DNA synthesis pathway
    - may modulate the susceptibility of subjects to several conditions
      - including ca

Beneficial effects of folate…

- Possible mechanisms (3)
  - folate deficiency
    - may induce complete transformation of deoxyuridylate monophosphate to deoxythymidylate monophosphate
      - which induces misincorporation of uracil into DNA
      - leads to chromosomal breaks and mutations

Beneficial effects of folate…

- Possible mechanisms (4)
  - folate deficiency
    - may cause abnormal methylation of DNA,
    - leading to alterations in expression of
      - critical protooncogenes
      - & tumor suppressor genes
  - Experiments in vivo on mice and dogs suggested
    - increased folate intake altered DNA methylation
    - & reduced the risks of ca

Joel et al. 1995….

Am. Association for Ca Research Journal

- **The effect of FA supplementation on the natural hx of CIN**
  - Multi center prospective, RCT
- 331 women with bx-proven koilocytic atypia, CIN I, CIN II
  - oral FA (5 mg) or a placebo daily for 6 mo
- Q 3 mo
  - Colpo,
  - Pap,
  - serum vitamin levels
    - folate, retinol, a-tocopherol, a-carotene, retinyl palmitate

Joel et al. 1995…

Am. Association for Ca Research Journal

- After 6 mo of tr:
  - no significant # between the 2 gps in the % of improvement
- Median serum folate levels at 3 & 6 mo
  - Tr arm (29.0 & 20.0 pg/dl)
  - Placebo arm (7.8 & 7.1 pg/dl)
- Serum levels of retinol, retinyl palmitate, a-tocopherol, a-carotene
  - not differ significantly between the two arms.
- Conclusion
  - FA (5 mg/d): no enhance the regression of early CIN
  - If correction of folate deficiency influence the CIN process and the outcome??

Eichholzer et al. 2001…

- **Folate and the risk of colorectal, Br, Cx ca**
  - How folate might protect against ca; not clear
    - Its role in DNA methylation and DNA synthesis?.
  - This study: Review of >30 studies
    - Long-term use of supplements of folate
      - Seems to be of greater benefit than dietary intake.
    - The effect of folate seems to be modulated by
      - Alcohol,
      - Methionine,
      - MTHFR polymorphisms

Eichholzer et al. 2001…

- Colorectal Ca
  - inverse association between intake/ levels of folate & colorectal ca
- Br ca
  - inverse association between folate intake and breast cancer among women who regularly consume alcohol.
- Cx Ca
  - uncertain for the role of folate in cervical cancer prevention

Galeone et al 2015

- **Folate intake & oral cavity and pharyngeal ca (OPC) (review)**
  - 10 case-control studies
  - 5,127 cases and 13,249 controls.
  - Inverse association between total folate intake and overall OPC risk
    - with a stronger association for oral cavity
  - The highest OPC risk ;in heavy alcohol drinkers with low folate intake as compared to never/light drinkers with high folate
  - protective effect of total folate intake on OPC risk

Yang et al (Am J Clin Nutr 2018)…

- **To evaluate the association of serum folate with the risk of CIN**
  - Firm associations between folate and CIN/ Cx Ca not established
- Shanxi province in northern China
  - Highest incidence of NTD and highest incidence of Cx Ca
    - Cx Ca 10 times > the national average
    - role of folate in reducing NTD is well accepted
- little studies: the interaction between HPV & folate in the risk of CIN

Yang et al. (Am J Clin Nutr 2018)…

- 2304 women aged 19–65 y
- serum folate concentration
  - not associated with CIN1 risk
  - inverse linear relation with HG-CIN
- The highest risk of CIN2+ :
  - Serum folate is inversely associated with the risk of HG CIN
    - in Chinese women(± hr-HPV)
  - maintenance of normal serum folate levels may be important for reducing the risk of CIN

Dong et al. 2020…

- **Enhanced Anti-Ca Effect of ATO + RT in Cx Ca**
- Olaparib (PARP inhibitor) involved in
  - preventing the release of PARP from RT-induced damaged DNA
  - to potentiate the effect of RT.
- Radiosensitization mechanism of Olaparib nanomedicine is unclear.
- Study:
  - on nude mice using cx ca xenograft models.

Dong et al. 2020…

- Results:
  - folate-conjugated active targeting olaparib nanoparticles (ATO) + RT
    - significantly inhibited tumor growth
    - significantly prolonged survival time of tumor-bearing mice.
- ATO (in this study) may represent
  - a novel formulation for olaparib delivery
  - promising potential for treating tumors
    - with an over-expression of folate receptors

Yacong Bo et Al. 2020 (Meta-Analysis)

- **Review of:**
  - 108 articles
  - 133 meta-analyses (observational Studies)
  - 154 meta-analyses (RCT)
- Current evidence:
  - Beneficial effects of folate:
    - Decrease in the all-cause mortality rate
    - Decrease in a No. of chronic diseases, including several ca
  - Adverse effect of folate:
    - Increased risk of prostate ca
    - Increased risk of, colorectal adenomatous lesions, asthma, wheezing, depression


Thank
you