Risk Factors of Gynecological Malignancies

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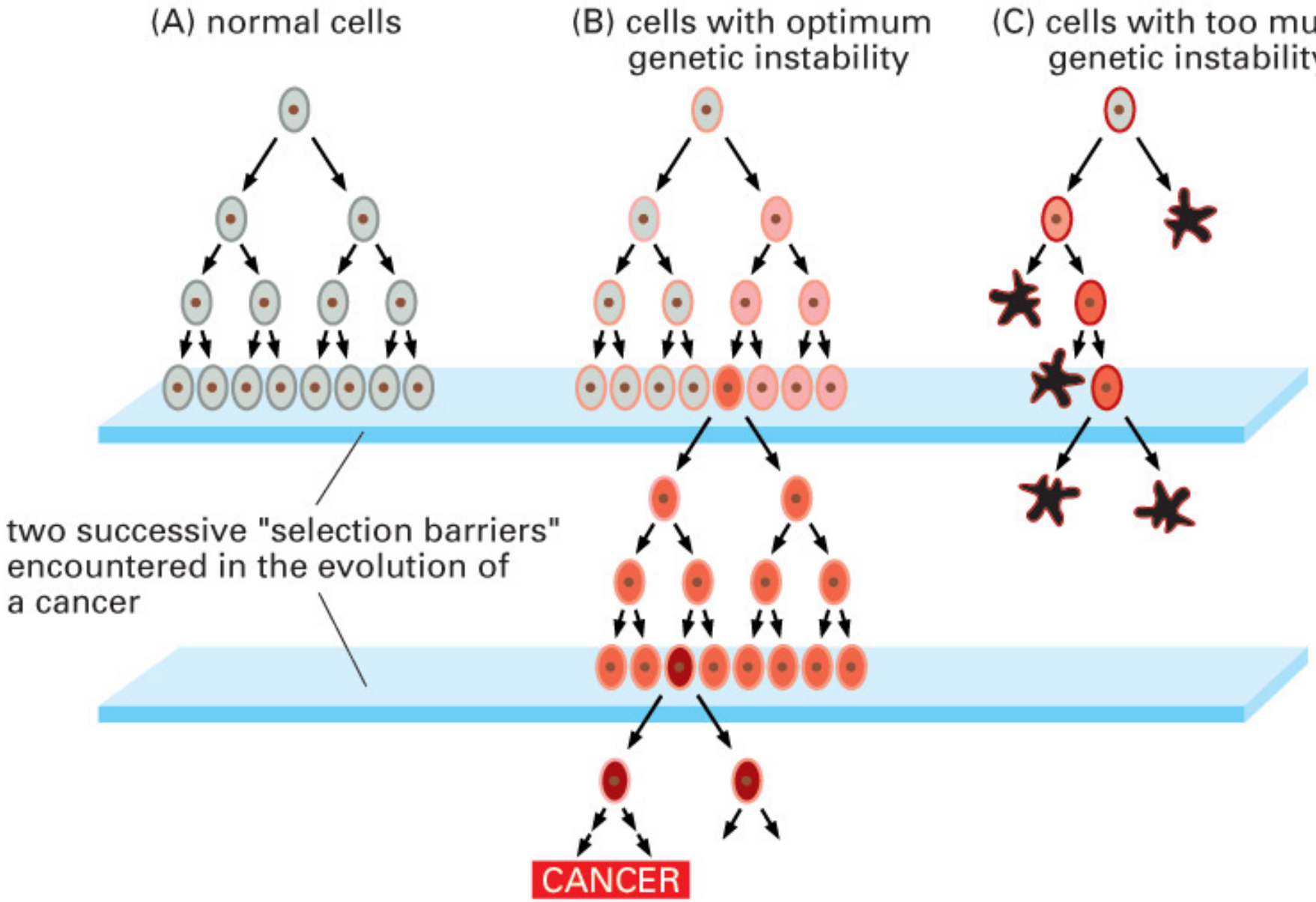


Figure 23–13. Molecular Biology of the Cell, 4th Edition.

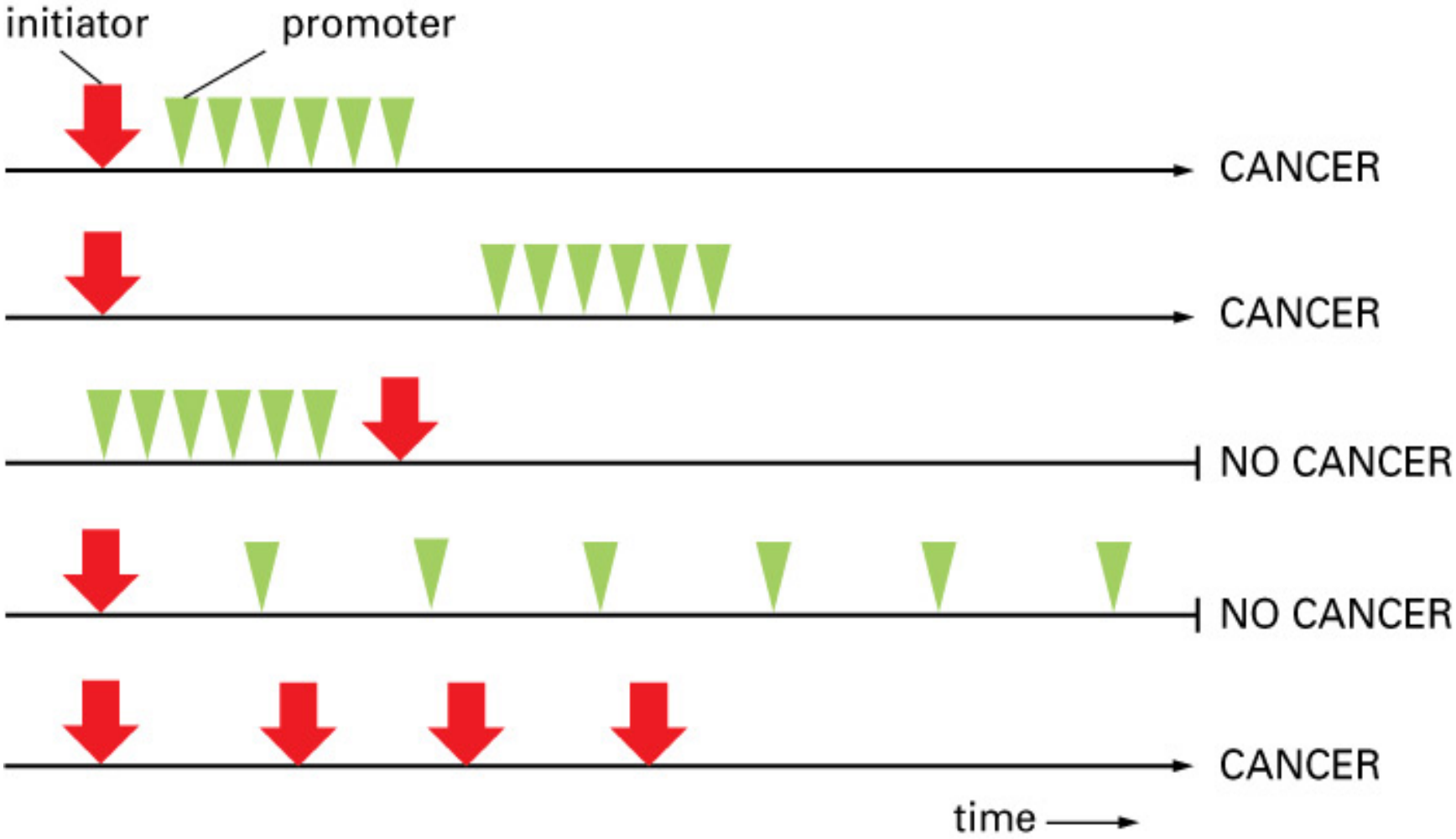


Figure 23–19. Molecular Biology of the Cell, 4th Edition.

- **Mutations accumulate over time**
- **Cancer incidence increases sharply with age**

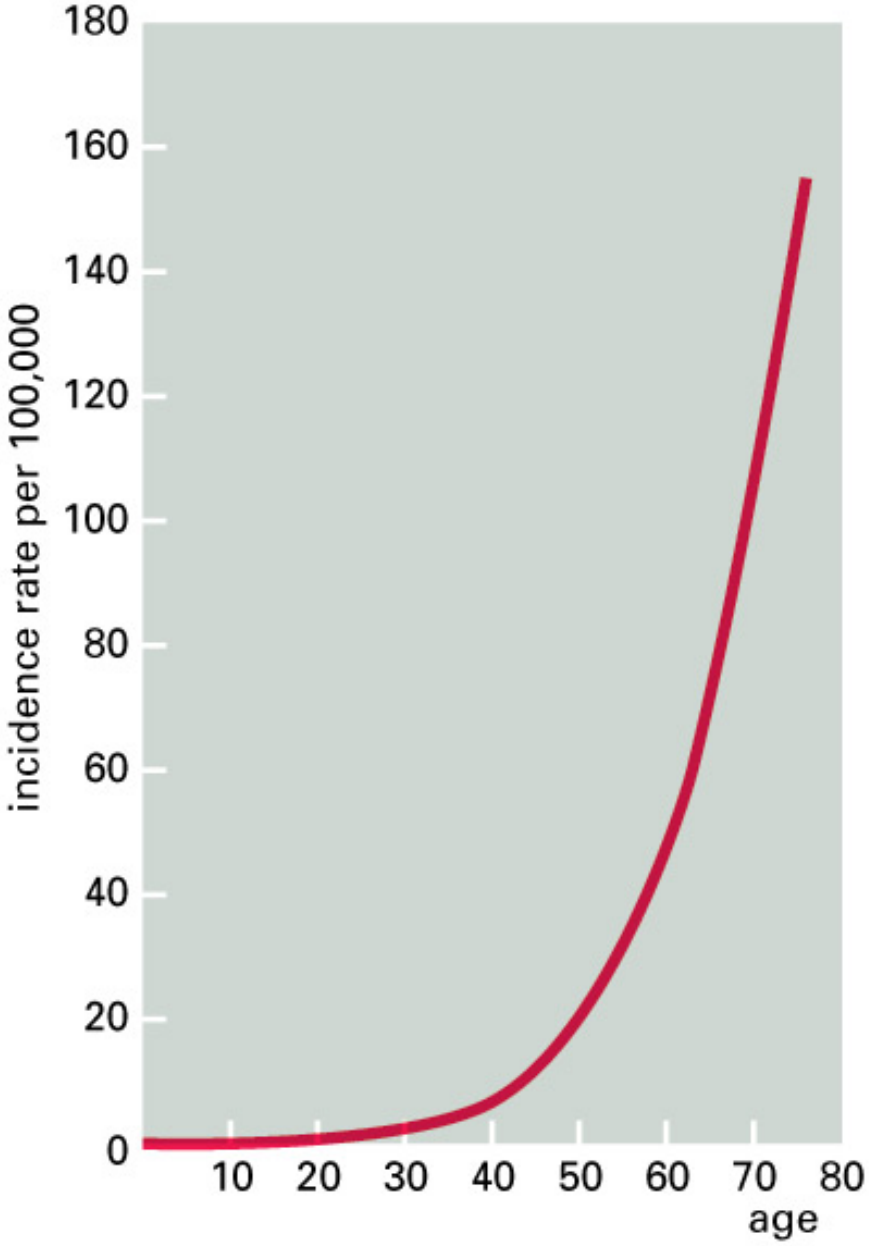


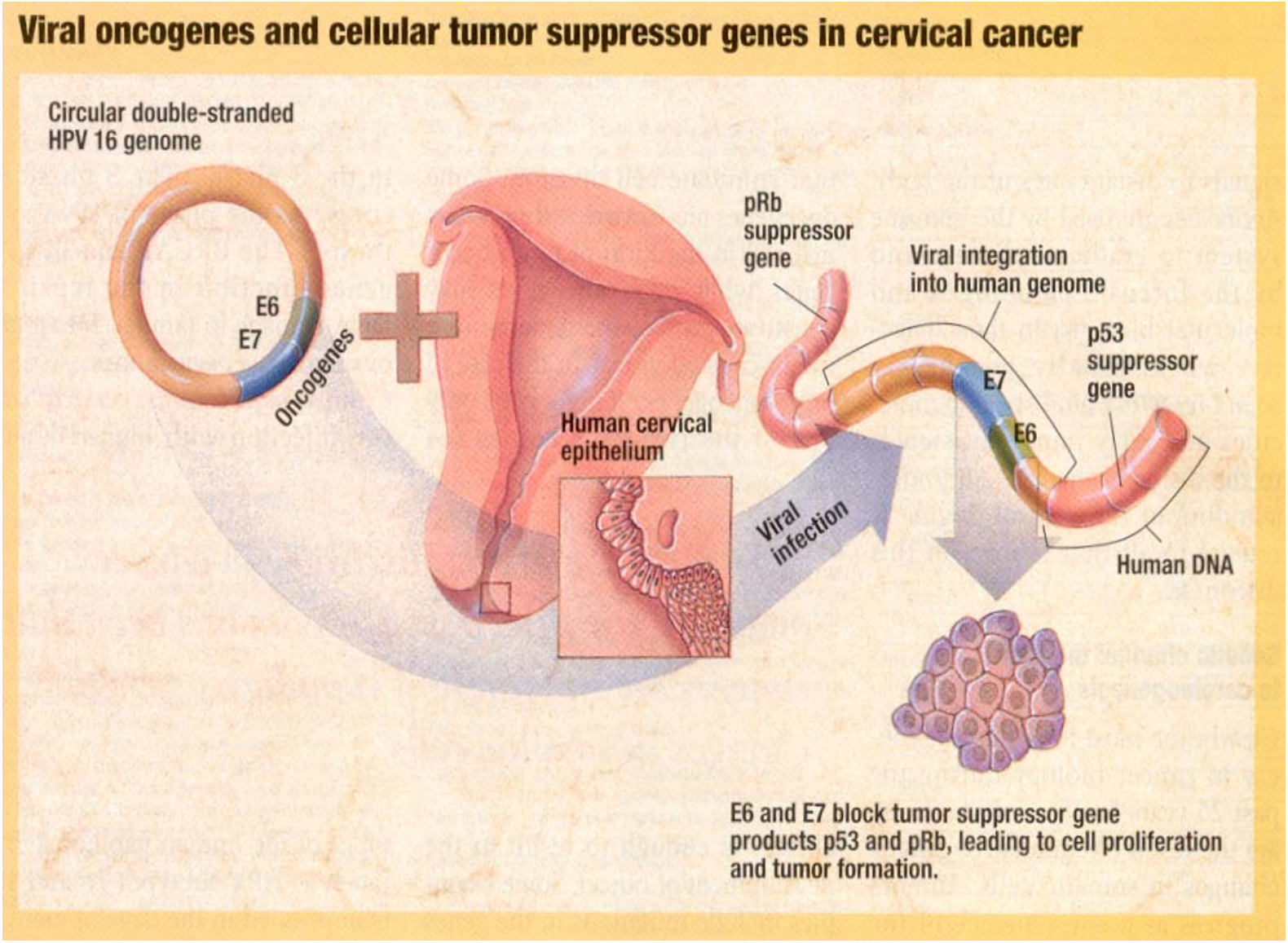
Figure 23–7. Molecular Biology of the Cell, 4th Edition.

Cervical Cancer

Cervical Cancer: Risk Factors

- **Persistent infection with high risk human papilloma virus (HPV)**
- **Three or more lifetime sexual partners.**
- **First sexual intercourse before age of 18**
- **Smoking**

- **A previous abnormal Pap smear**
- **Never having had a Pap or not having one in the previous 5-10 years**



Tewari et al Contemporary OB/GYN Feb, 2001.

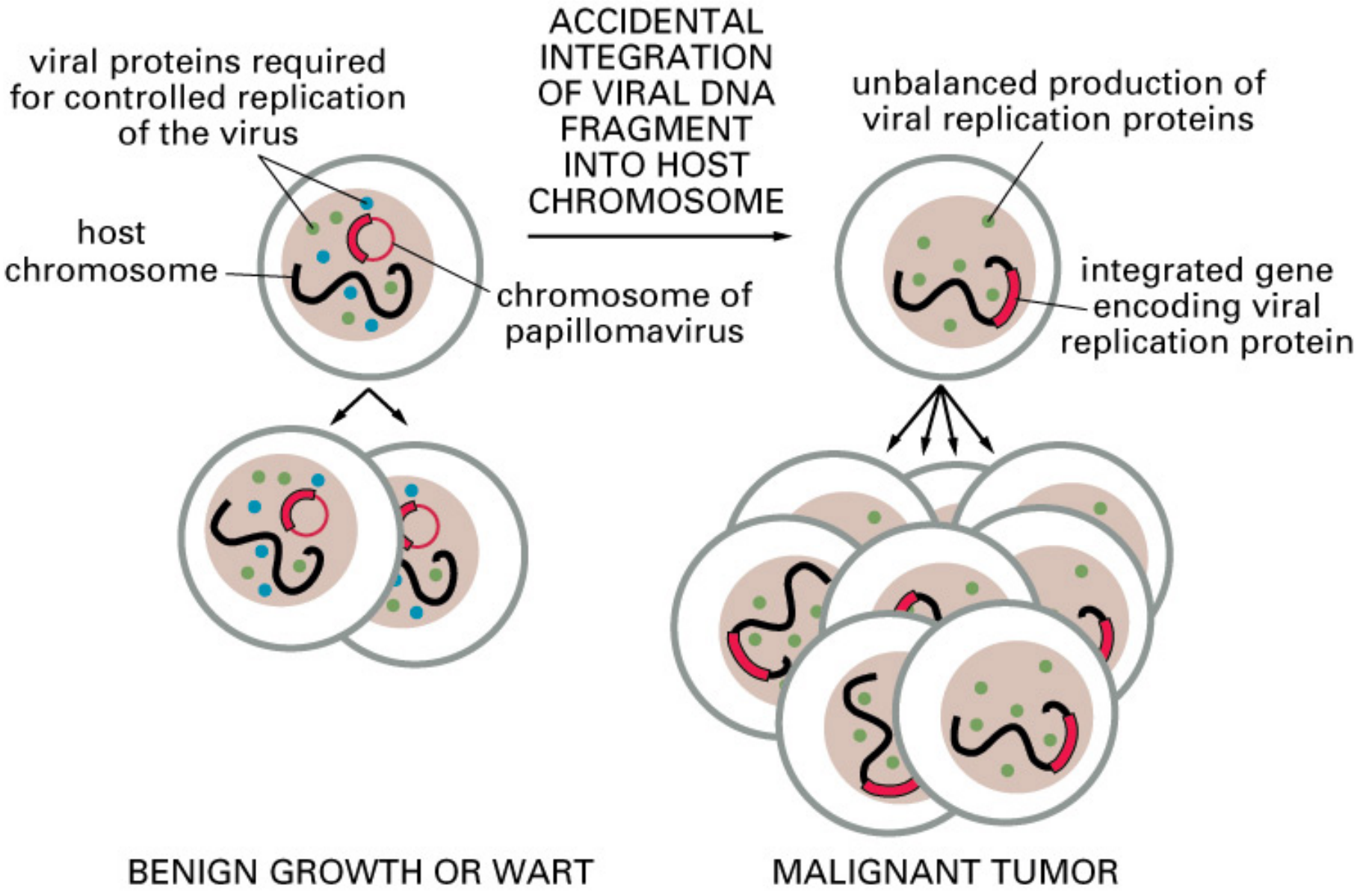


Figure 23–34. Molecular Biology of the Cell, 4th Edition.

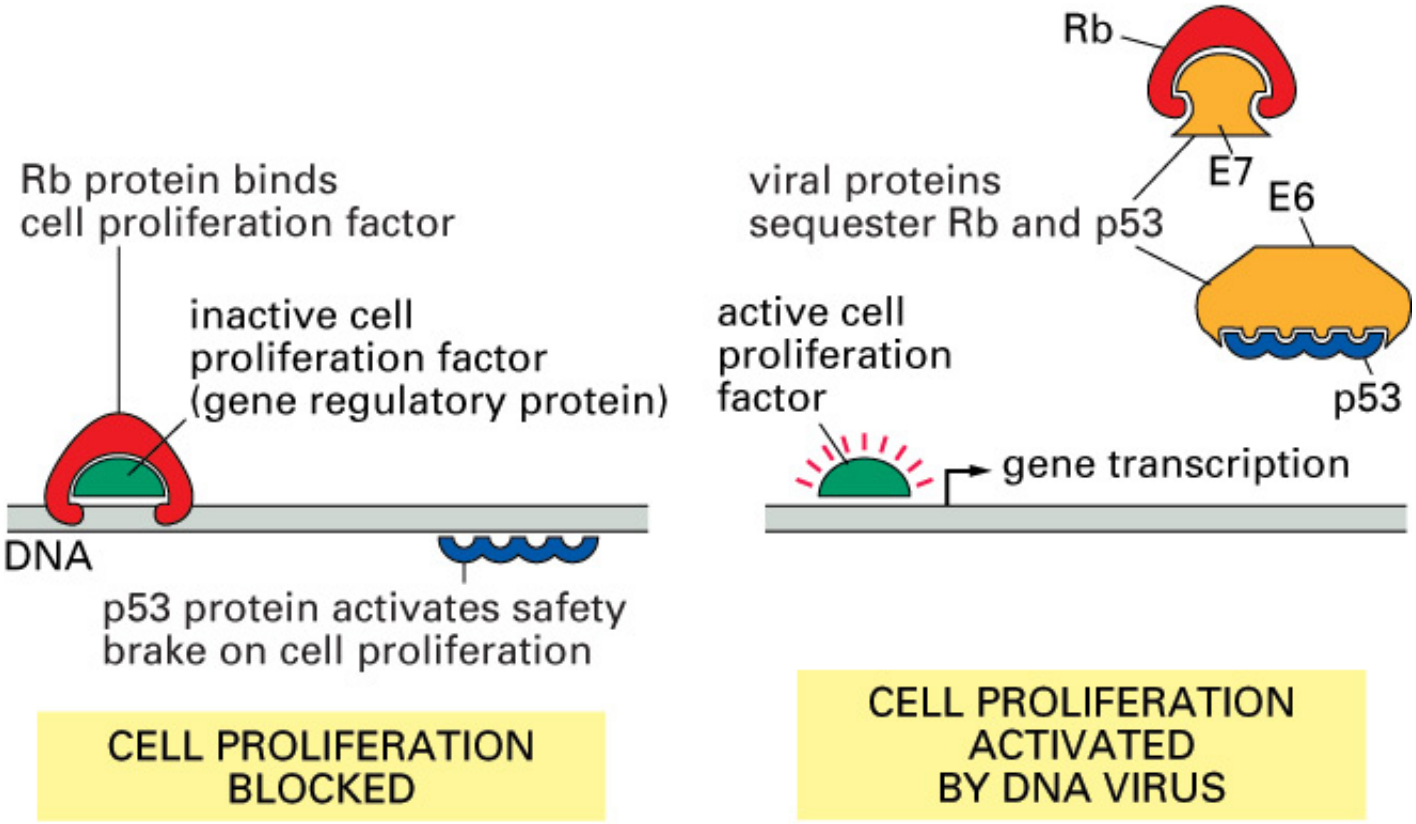


Figure 23–35. Molecular Biology of the Cell, 4th Edition.

Cervical cancer development

HPV infection

(necessary cause)

+

Co factors

(contributing factors)

- Viral load
- Smoking
- Genetic susceptibility

etc.

HPV and Cervical Cancer

- Risk depending on HPV detection technique
  - Schiffman et al.

    : lower estimate of the relative risk in Southern blot than the more sensitive PCR approach.
  - Bosch et al.

    : using Virapap; OR, 6.3; 95% CI, 3.4–11.6),

    using Southern hybridization; OR, 16.3, 95% CI, 7.7–34.4

    using PCR; OR, 24.3, 95% CI, 14.4–41.0

HPV and Cervical Cancer

- Importance of using the most sensitive molecular analysis in molecular epidemiology
- The more sensitive, the more accurate estimation is possible for relative risk and attributable risk fractions are to be made

HPV viral load and CIS

- *Viral load of human papilloma virus 16 as a determinant for development of cervical carcinoma in situ: a nested case-control study.* Josefsson AM et al. Lancet. 2000;355(9222)

Categories*	Mean HPV C_t	
	Cases/controls	Odds ratio (95% CI)†
HPV negative	212/464	1·0
HPV positive, C_t 44·8–50·0	27/32	2·0 (1·1–3·8)
HPV positive, C_t 41·25–44·8	41/18	4·4 (2·3–8·3)
HPV positive, C_t 38·99–41·25	48/12	8·1 (3·8–17·3)
HPV positive, C_t 36·66–38·99	52/7	18·7 (7·1–49·5)
HPV positive, C_t <36·66	58/2	68·8 (15·8–299·6)

*Calculated on each 20th percentile of distribution of mean HPV 16 C_t value for each woman. †Adjusted for β-actin.

HPV viral load and CIS

Interpretation

- Analysis of the amount of HPV DNA can predict cancer risk at a stage when current screening methods are uninformative.

- Testing for the amount of HPV 16 DNA might improve our ability to distinguish between infections that have a high or low risk of progressing into cervical cancer.

Smoking and CIN

- *Cigarette Smoking, Oncogenic Human Papillomavirus, Ki-67 Antigen, and Cervical Intraepithelial Neoplasia.*

Tiffany et al. Am J Epidemiol 2004

TABLE 2. Odds ratios and 95% confidence intervals for the associations between smoking history and CIN1* and between smoking history and ≥CIN2–3,* Planned Parenthood of Western Washington and Harborview Medical Center Women's Research Clinic, December 1997–December 2001

	Negative (*n* = 181)		CIN1 (*n* = 137)		≥CIN2–3 (*n* = 143)		CIN1 vs. negative		≥CIN2–3 vs. negative	
	No.	%	No.	%	No.	%	Adjusted OR*,†	95% CI*	Adjusted OR†	95% CI
Smoking status										
Never	90	50	54	39	57	40	1.0		1.0	
Former	22	12	18	13	24	17	1.7	0.8, 3.6	2.0	0.9, 4.1
Current	69	38	65	48	62	43	1.8	1.1, 3.1	1.6	1.0, 2.7
No. of cigarette pack-years										
<0.1	90	50	54	39	57	40	1.0		1.0	
0.1–5	66	36	63	46	53	37	1.7	1.0, 2.8	1.4	0.8, 2.4
>5	25	14	20	15	33	23	2.1	1.0, 4.5	2.6	1.3, 5.2
No. of cigarettes/day										
0	97	54	60	44	62	43	1.0		1.0	
1–10	62	34	54	39	55	39	1.4	0.9, 2.5	1.4	0.8, 2.4
>10	22	12	23	17	26	18	2.5	1.2, 5.3	2.6	1.3, 5.5

Smoking and CIN

- Smoking : confounded by smokers having more or different sexual partners ?

- Smoking increased the risk of subsequent detection of cervical intraepithelial neoplasia in women with HPV infection.

- These findings strengthen the evidence that smoking may be one of causes cervical cancer.

Cervical cancer Candidate SNPs

- p53 Codon 72 Polymorphism
- interleukin-18 gene promoter polymorphism
- Fas-670 gene
- human leukocyte antigen polymorphism
- CD83 gene polymorphism
- cyclooxygenase-2 and inducible nitric oxide synthase gene polymorphism
- matrix metalloproteinase(MMP)-1 promoter polymorphism

TP53 codon 72 SNP and cervical cancer

- **pooled analysis of individual data from 49 studies**
- No association was found between cervical cancer and TP53 codon 72 polymorphism when the analysis was restricted to methodologically sound studies

Lancet Oncol. 2009;10(8):772-84.

Nutrition and cervical cancer

Vitamin or anti-oxidant intake and risk of cervical neoplasm: a meta-analysis (in preparation for submission)

- This study was aimed at investigating those quantitative effects on cervical neoplasm using meta-analysis.
- **Methods:** We searched MEDLINE (PubMed), EMBASE, and the Cochrane Review in November 2008

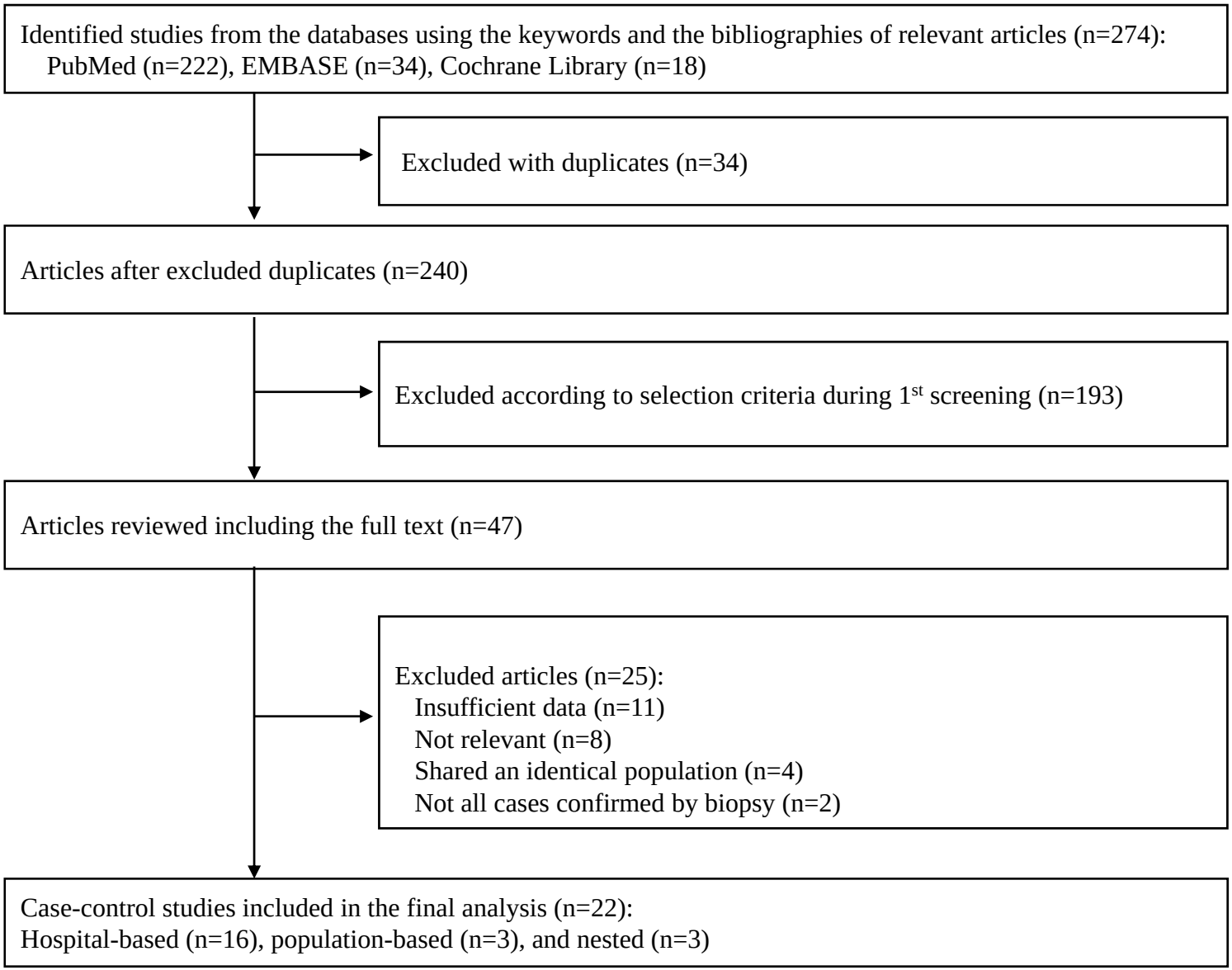
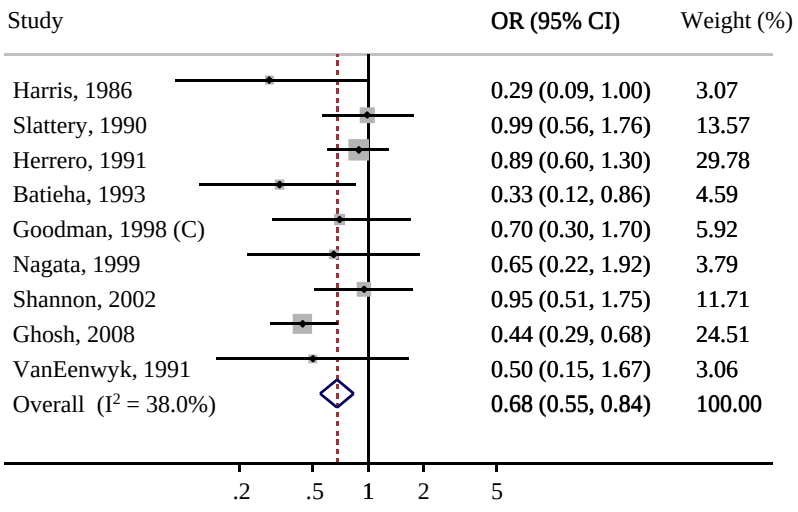


Figure 1. Flow diagram of identification of relevant studies.

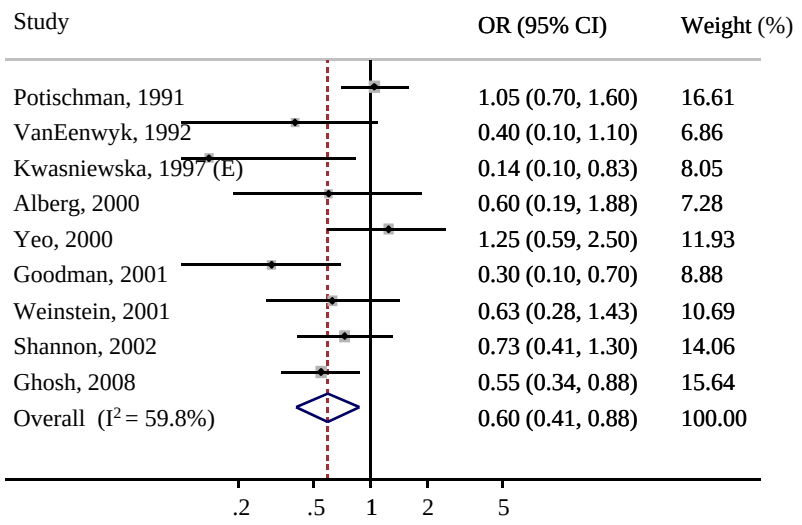
Vitamin and cervical neoplasia

(unpublished data)

A. Beta-carotene (n = 9)*



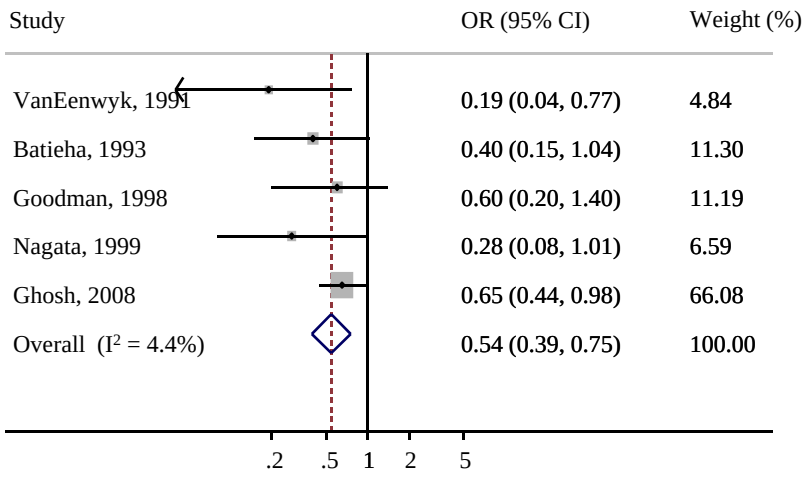
B. Folate (n = 9)†



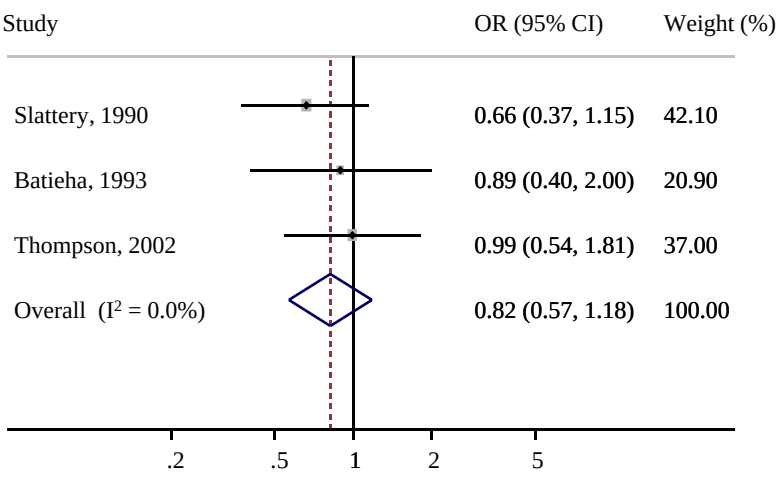
Vitamin and cervical neoplasia

(unpublished data)

C. Lycopene (n = 5)*



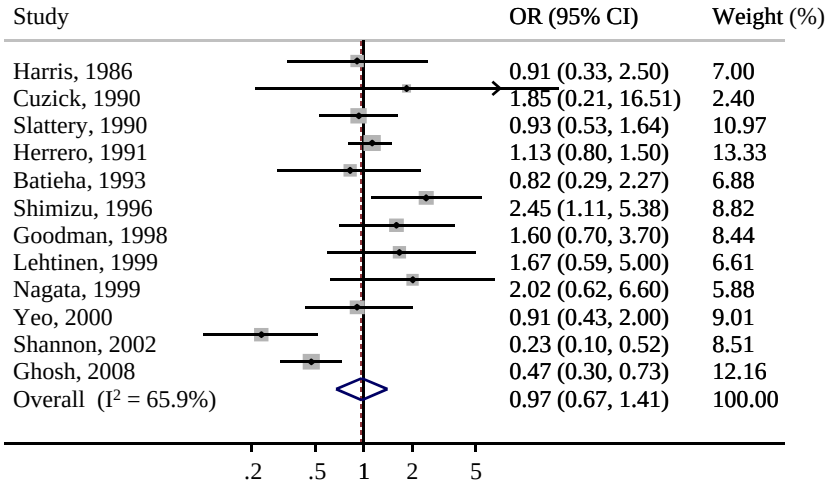
D. Selenium (n = 3)*



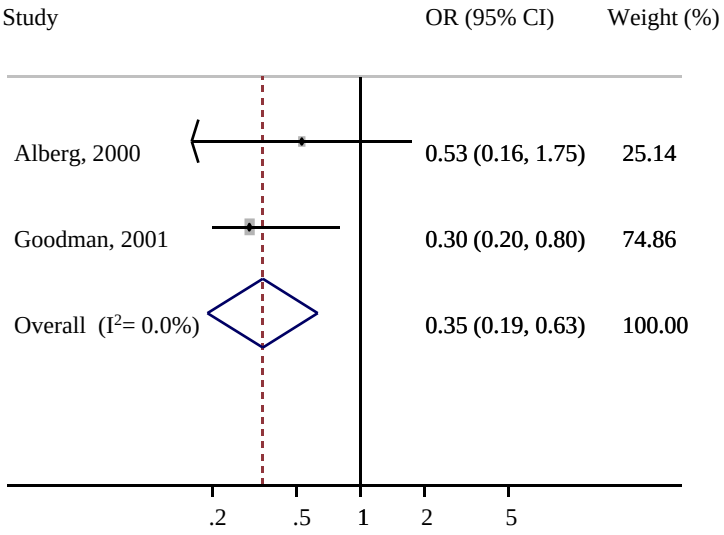
Vitamin and cervical neoplasia

(unpublished data)

E . Vitamin A (n = 12)†



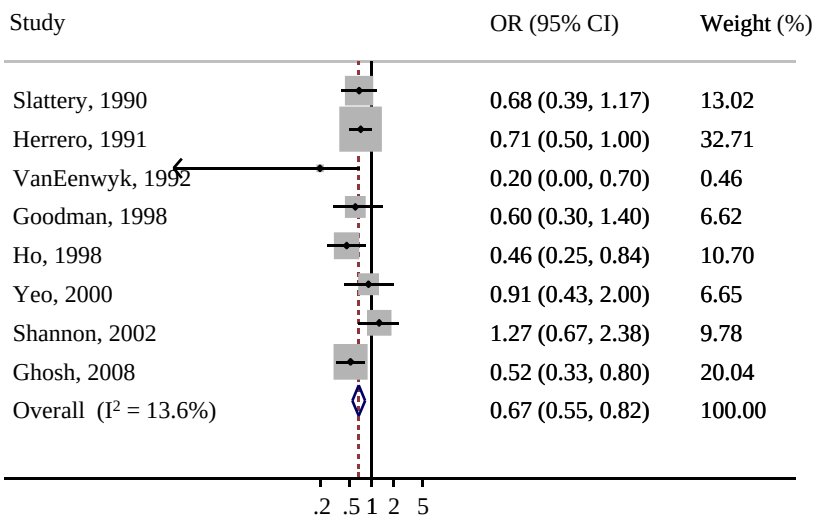
F. Vitamin B12 (n = 2)*



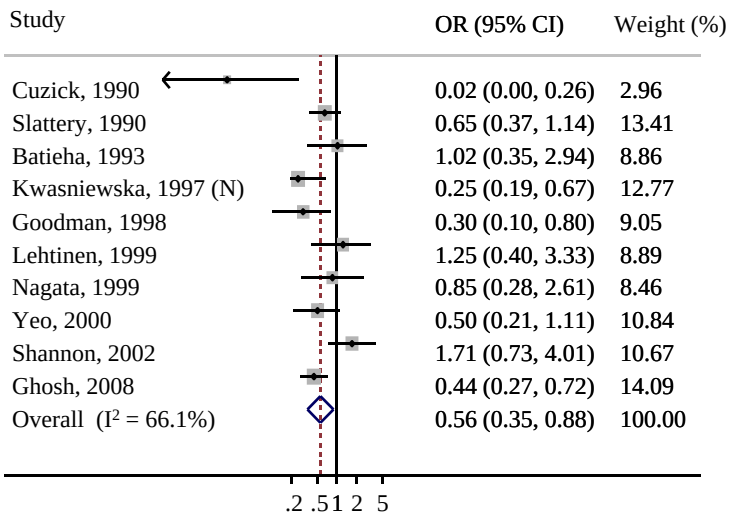
Vitamin and cervical neoplasia

(unpublished data)

G. Vitamin C (n = 8)*



H. Vitamin E (n = 10)†



Ovarian Cancer

Risk Factors for Ovarian Cancer

Increased Risk	Decreased Risk
Age	Oral Contraceptive Use
Family history	Pregnancy and Breastfeeding
Infertility/low parity	Tubal ligation
Personal cancer history	Hysterectomy/Removal of Both Ovaries

Gynecologic Cancer Foundation

Ovarian cancer

Decreasing Risk=Prevention

Effect of Parity

Term Pregnancies	RR
0	1
1	0.6
2 or 3	0.5
4 or more	0.33

Ovarian cancer

Decreasing Risk=Prevention

Effect of OCPs

Duration of use	RR
Never	1
3mos-4yrs	0.65
5-9 yrs	0.4
10 yrs or more	0.2

Ovarian cancer

Increase Risk Factor

BRCA1	35-45%
BRCA2	15-25%

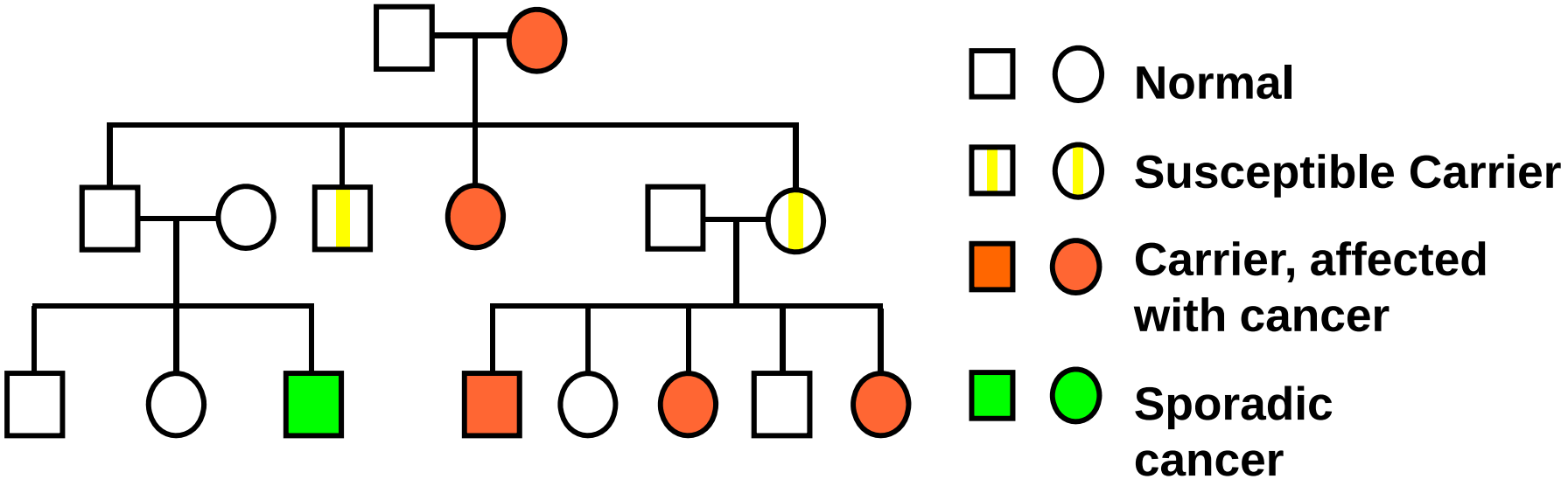
If reproduction is not an issue, offer BSO.

Hereditary Ovarian Cancer

Familial breast cancer, type 1	Breast cancer	**Ovarian cancer**	**BRCA1**	17q21	Repair of double-strand DNA breaks?
Familial breast cancer, type 2	Breast cancer	Pancreatic cancer, breast cancer in males, **Ovarian cancer**	**BRCA2**	13q12	Repair of double-strand DNA breaks?
Hereditary nonpolyposis colorectal cancer	Colorectal cancer	**Endometrial, Ovarian**, hepato-biliary, and bladder cancer, glioblastoma (Turcot syndrome)	**MSH2** **MLH1** **PMSL1** **PMSL2** **MSH6**	2p22-p21 3p21 2q31.1 7p22 2p16	Repair of DNA base-pair mismatches. Maintains stability of simple tandem repeats of DNA

From Thompson & Thompson, 6th edition, Table 16-1, page 314

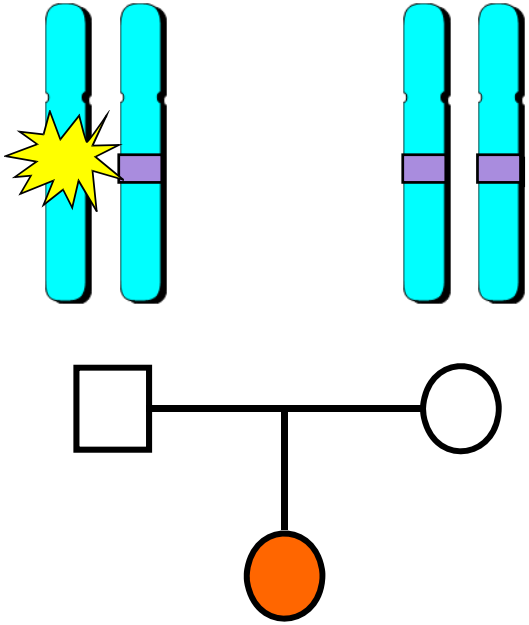
Most Cancer Susceptibility Genes: Dominant With Incomplete Penetrance



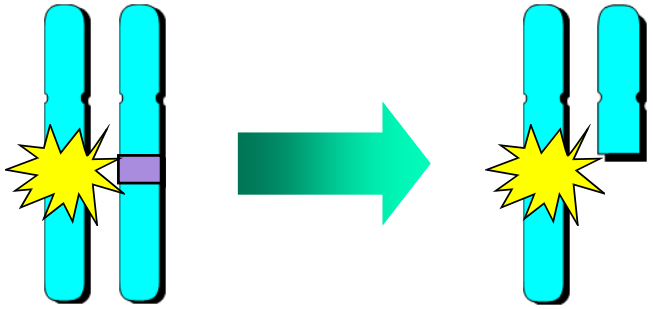
- Penetrance is often incomplete
- May appear to “skip” generations
- Individuals inherit altered cancer susceptibility gene, not cancer

Knudson Two-Hit Hypothesis

First hit

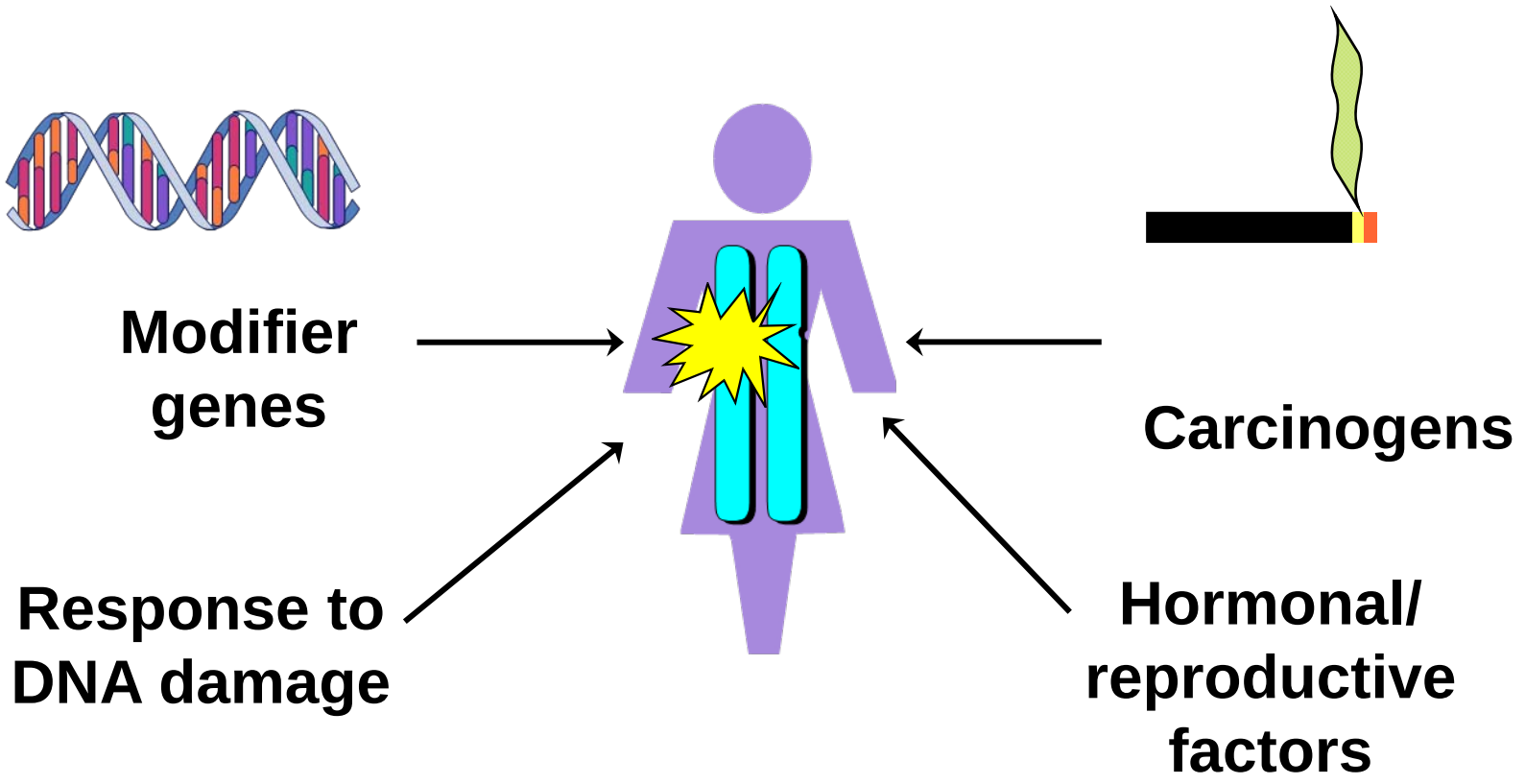


First hit in germline of child



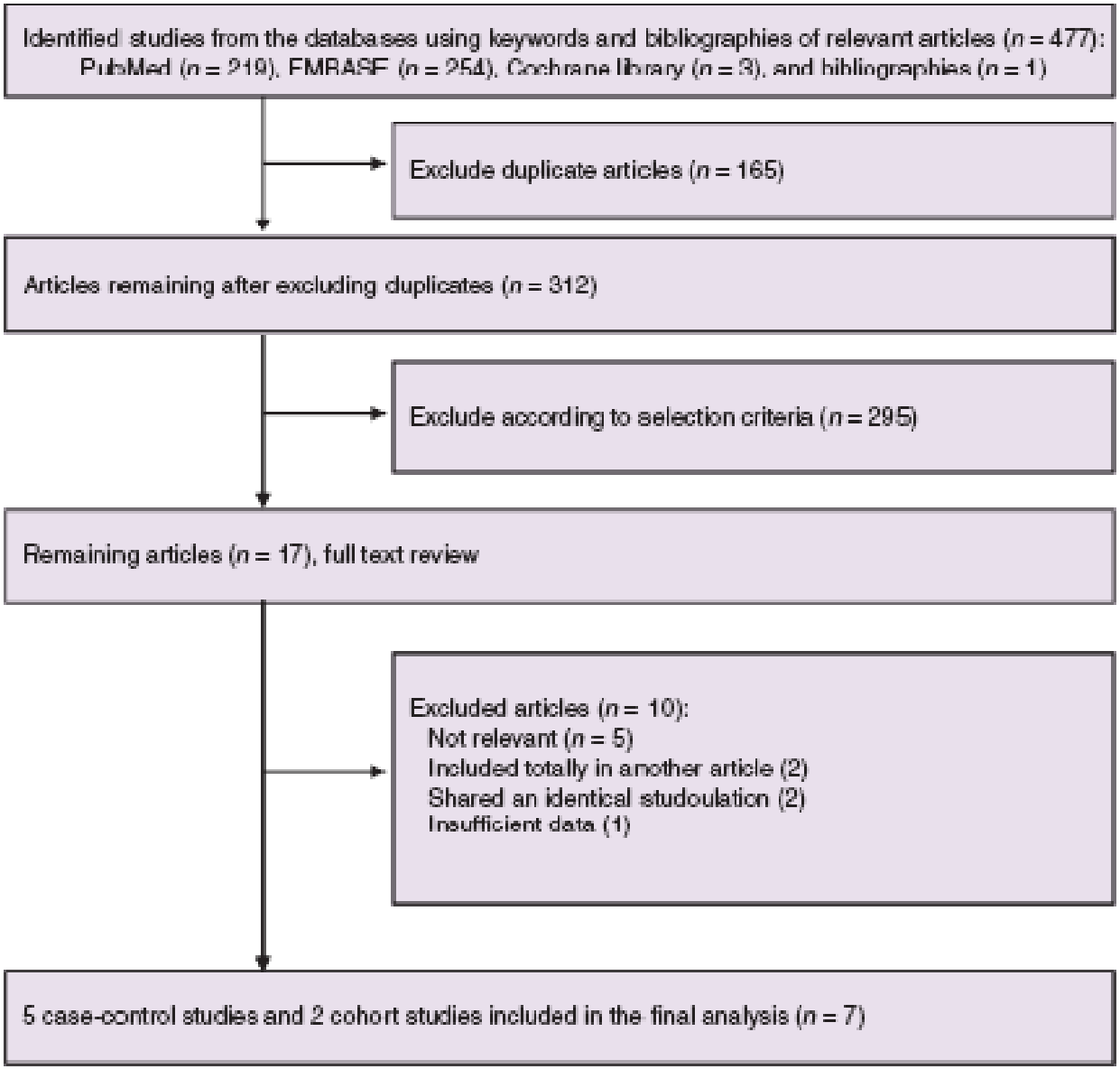
Second hit (tumor)

Factors Affecting Penetrance



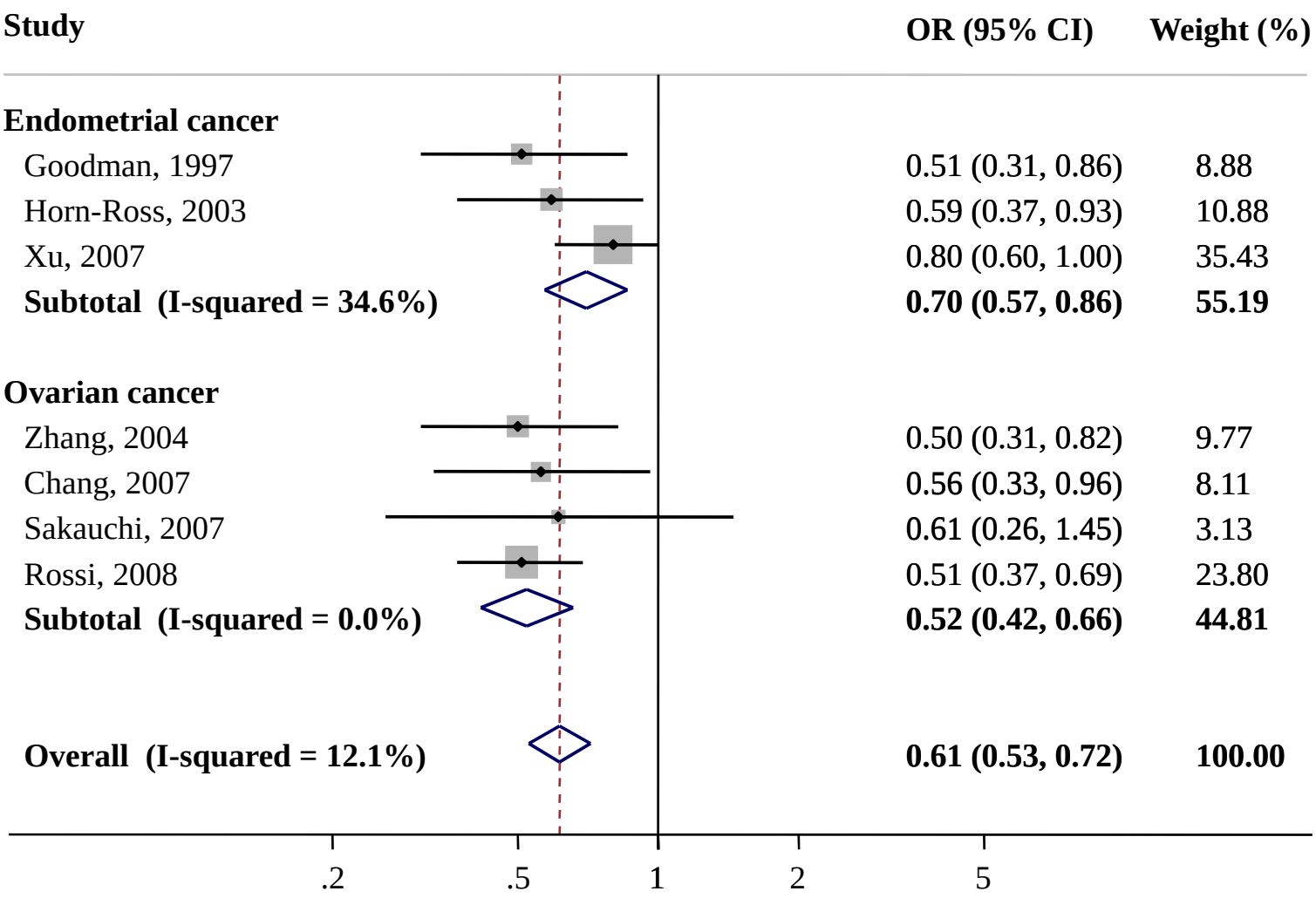
Not everyone with an altered gene develops cancer

Soy intake and risk of endocrine-related gynaecological cancer: a meta-analysis



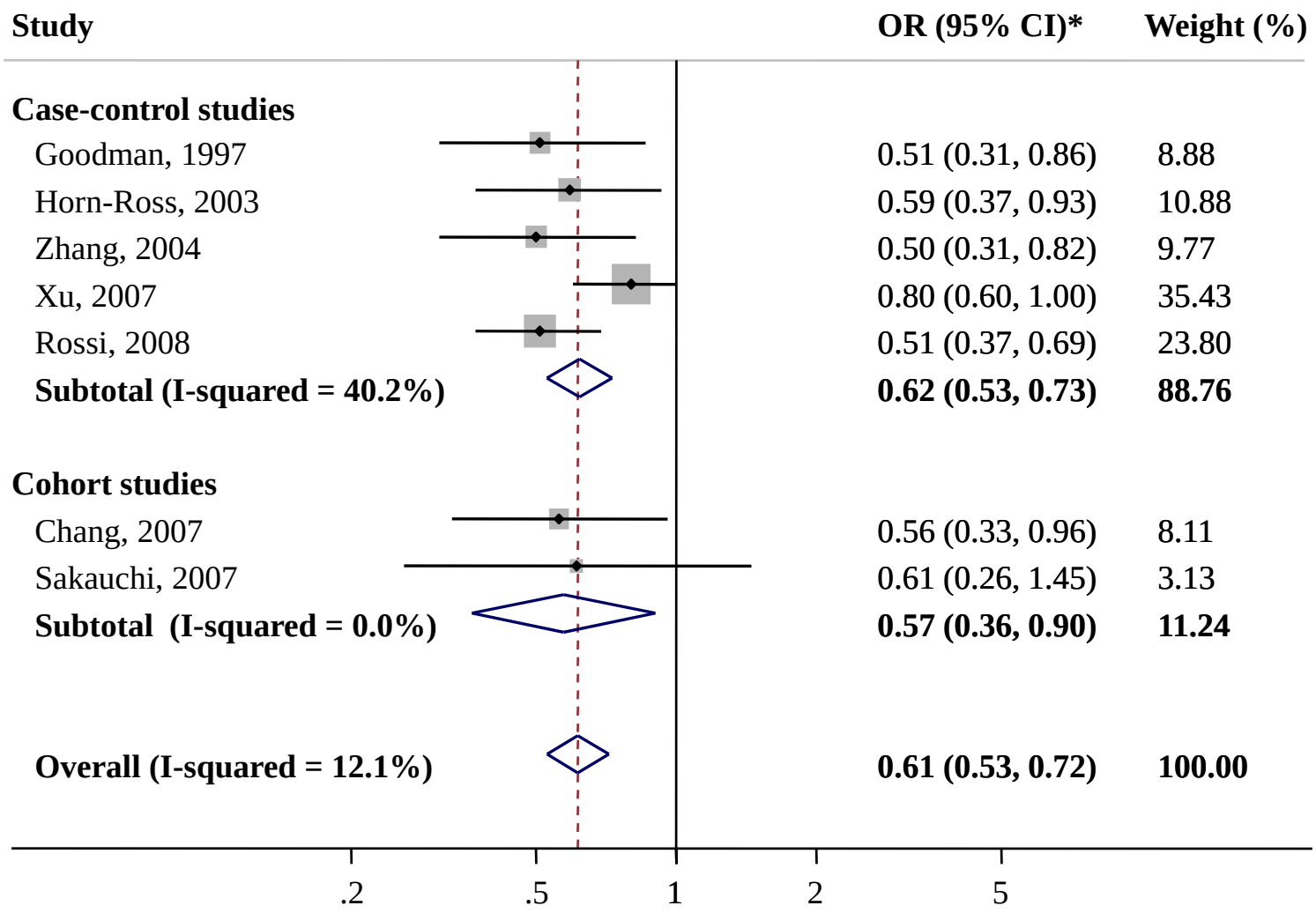
BJOG, 2009

FIGURE 2. Soy intake and the risk of endocrine-related gynecological cancers by type of cancer in a meta-analysis of epidemiologic studies (n=7)



*** Fixed-Effects Model. OR, Odd Ratio; CI, Confidence Interval.**

FIGURE 3. Soy intake and the risk of endocrine-related gynecological cancers by study design in a meta-analysis of epidemiologic studies (n=7)



*** Fixed-Effects Model. OR, Odd Ratio; CI, Confidence Interval.**

Table 3. Dose-response relationship between soy intake and the risk of endometrial cancer or ovarian cancer in subgroup meta-analyses*

Category of soy intake (vs lowest)	No. studies	Summary OR (95% CI)	Heterogeneity, I^2	Model used	*P* for trend**
Lower	7	0.94 (0.83–1.06)	34.1%	Fixed-effects	0.025
Moderate	5	0.77 (0.65–0.91)	45.3%	Fixed-effects	
Highest	7	0.61 (0.53–0.72)	12.1%	Fixed-effects	

*Highest intake was defined as quintile 5, quartile 4 or tertile 3; moderate intake as quintile 4 or quartile 3; lower intake as quintile 2, quartile 2 or tertile 2, respectively, based on each study's categorization. **A weighted linear regression was performed to model the natural logarithm of OR for the risk of endometrial cancer or ovarian cancer as a function of qualitatively described soy intake (lower = 1, moderate = 2 and highest = 3) using the inverse variance calculated from confidence intervals of each category; standard error = (LN(upper limit) – LN(lower limit))/2 x 1.96; inverse variance = 1/(standard error x standard error).

声の出演：ペ・ヨンジュン　チェ・ジウ

メイキング・オブ・アニメ 冬のソナタ

～再び始まる物語～

Endometrial Cancer

Endometrial cancer

Increased risk factors
- Age
- Estrogen
  - Obesity
  - Diabetes (Type II)
  - PCOS
  - Late menopause (>55yr) (Define menopause)
  - Nulliparity
- Tamoxifen
- Hereditary nonpolyposis colorectal cancer (HNPCC)

Endometrial cancer

• **Overweight**	**10.0**
• **Nulliparity**	**2.0**
• **Diabetic**	**2.7**
• **Unopposed estrogen**	**6.0**
• **Tamoxifen**	**2.2**
• **Combined OCPs**	**0.5**

N Engl J Med. 1996 ;335(9):640-9

Endometrial cancer

Decreased risk factors:

--Add progestin to ERT (RR=1)
--Use of OCPs for at least 12 mos
(RR=0.5). Effect lasts at least
15 years.
--Exercise—decreases obesity and
favorable changes in immune function
and sexual and metabolic hormone levels and
growth factors
--Diet of fresh fruit, vegetables, whole grain foods

Endometrial cancer

Risk Factors

HNPCC (Lynch Syndrome II) is a mutation of “DNA mismatch repair” genes MLH1, MSH2 & 6, and PMS2 most often.

High risk for tumors of endometrium, ovary, stomach, small bowel, hepato-biliary system, urologic system.

In half of the women, endometrial and ovarian cancer PRECEDE colon cancer.

ELSEVIER

Cancer Genetics and Cytogenetics 172 (2007) 178–179

Cancer Genetics and Cytogenetics

Letter to the editor

Polymorphisms in CAG active allele length of the androgen receptor gene are not associated with increased risk of endometrial cancer

Table 1
Age at diagnosis of endometrial cancer according to the number of short alleles

Classified by the number of alleles with repeat length ≤ 22			
0 (n = 9)	1 (n = 17)	2 (n = 17)	
57.67 ± 10.67	64.65 ± 10.65	59.12 ± 8.86	F = 1.94, P > 0.05*
Linear −0.08 (−2.17, 2.01); P = 0.96**			
Classified by the number of active alleles with repeat length ≤ 22			
0 (n = 1)	1 (n = 19)	2 (n = 23)	
57.00 ± 0.00	62.53 ± 10.32	59.91 ± 10.37	F = 0.41, P > 0.05
Linear −1.64 (−4.52, 1.24); P = 0.57			

* By analysis of variance.

** By linear regression. Numbers in parentheses show 95% confidence interval.

Ju et al., 2007

Endometrial cancer

HNPCC should be considered if hx
- of three relatives with colorectal, endometrial, small bowel, urologic system

One first degree relative

Two successive generations

At least one under age 50.

Endometrial Cancer

- Women at risk for HNPCC
  - Annual endometrial biopsy at age 35

Summary

- Risk factors of gynecologic cancer
  - Well-established risk factors : HPV, BRCA mutation, HNPCC etc.
  - Cofactors altering the penetrance, changing individual susceptibility : viral load, SNP?, smoking, diet, life style etc.

Thank You for attention!

ありがとうございます