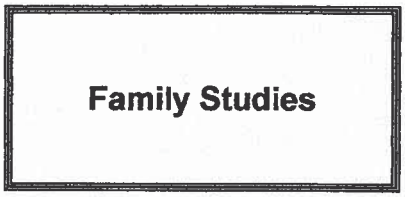
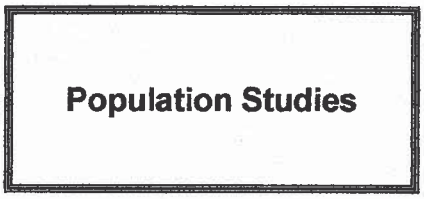
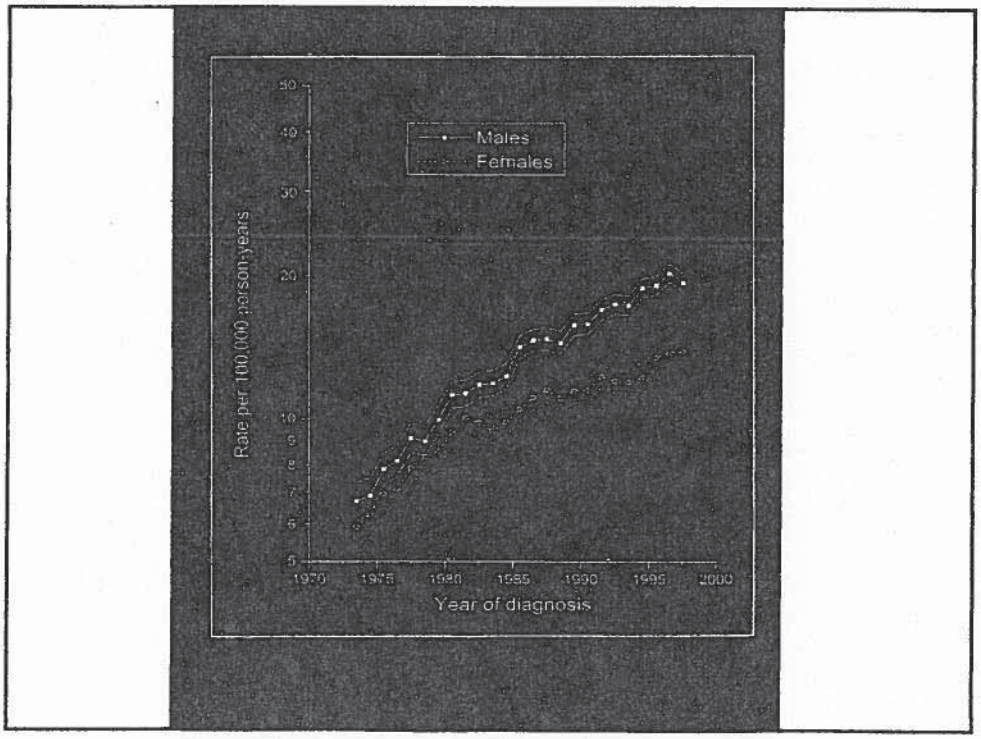
Genes and Susceptibility to Carcinogens: The Melanoma Story

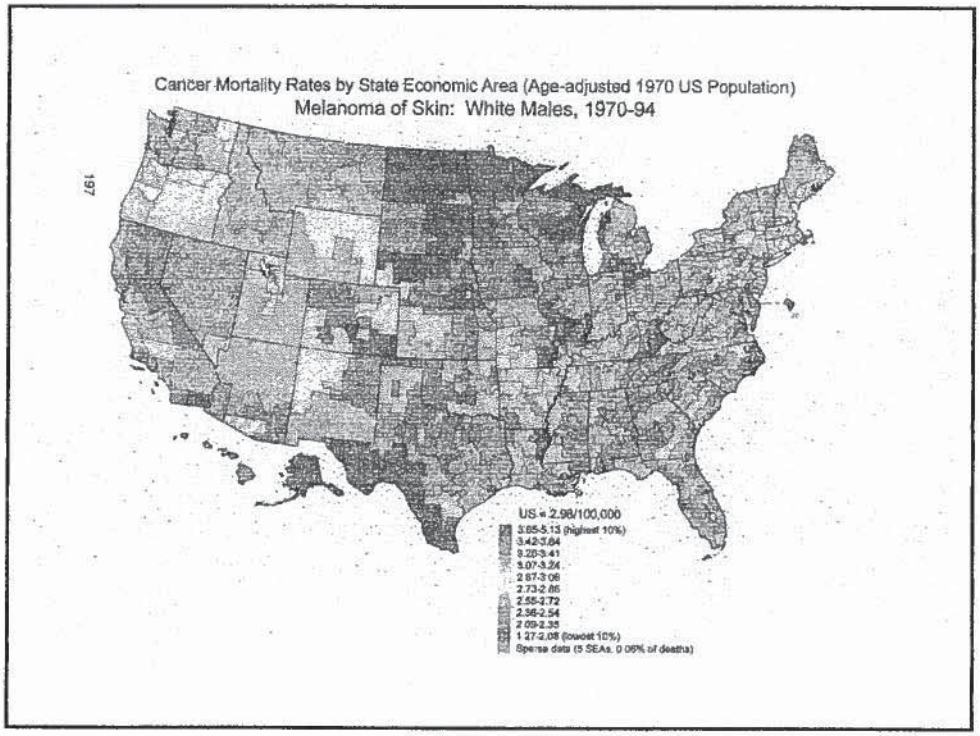




US Trends

- Family Studies
- Population Studies

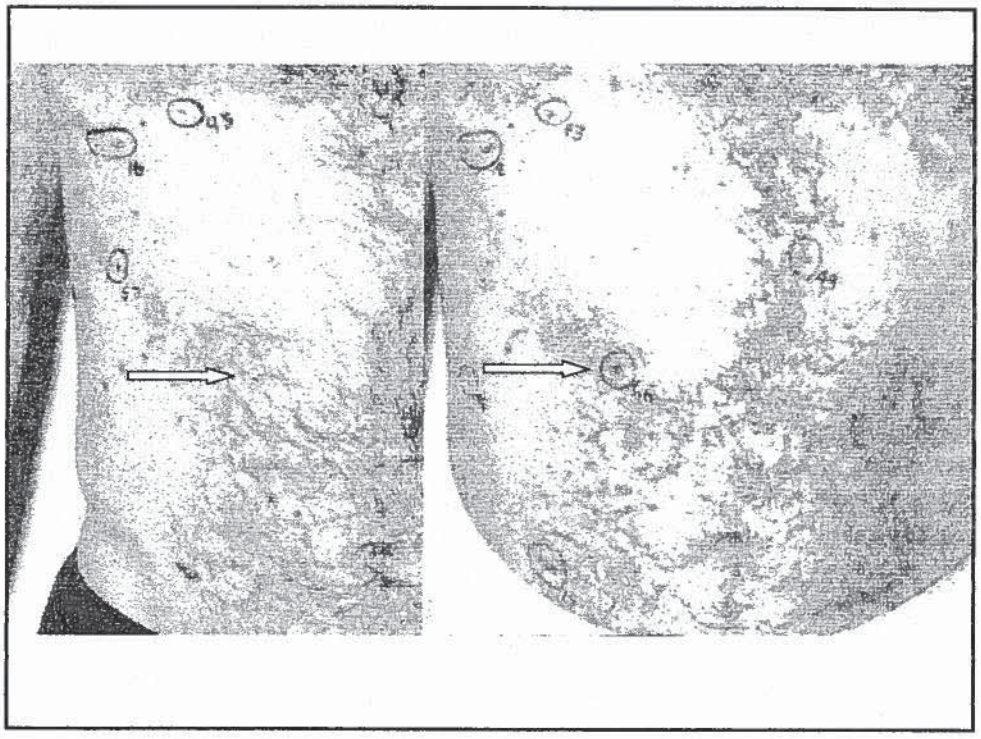


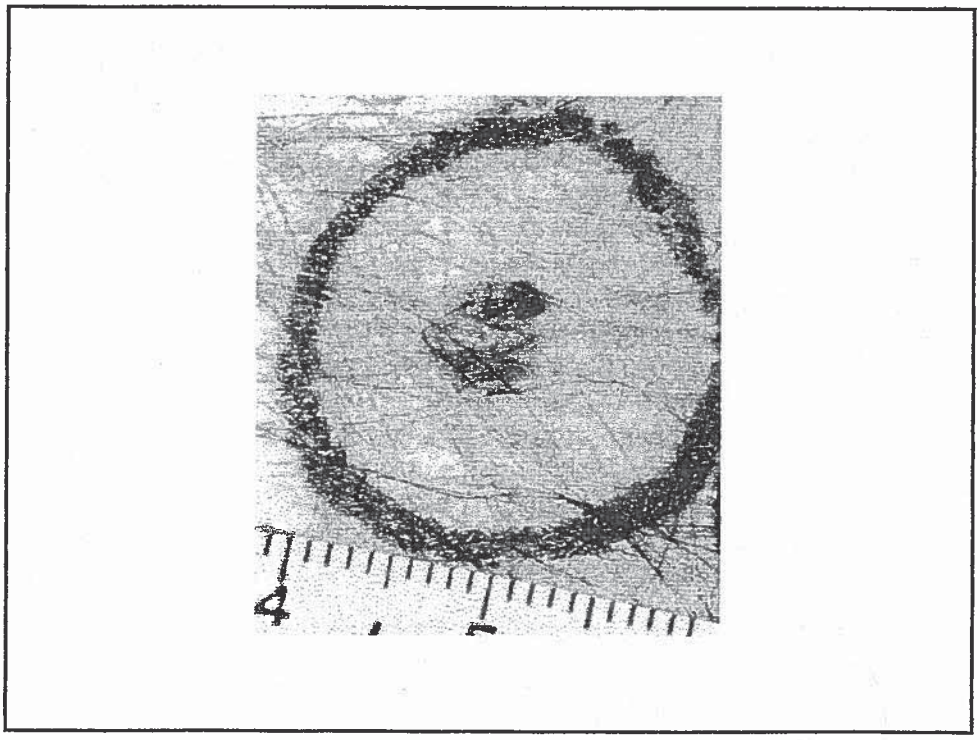


US Trends

Family Studies

Population Studies





Familial Melanoma

- Over 50 families with >1200 individuals fully evaluated
- Prospectively followed for up to 25 years
- Dysplastic nevi identified; natural history of melanocytic lesions described
- Clinical guidelines developed
- Two major susceptibility genes

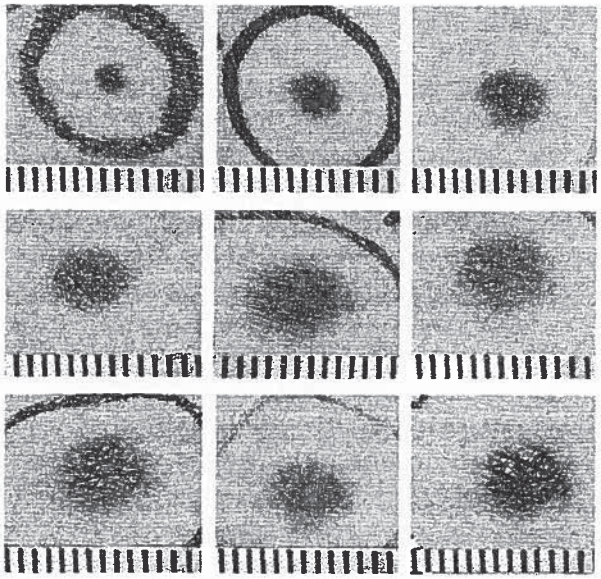
Major Susceptibility Genes

- *CDKN2A* - tumor suppressor
  - p16 alpha transcript (RB pathway)
  - $p14^{ARF}$ beta transcript (p53 pathway)
- *CDK4* – oncogene (RB pathway)
- Others being sought

Risk of melanoma

- Prospective risk of melanoma 35-70 fold increased
- Risk factors
  - Germline mutation in *CDKN2A* or *CDK4*
  - Dysplastic nevi
  - Sun exposure

Goldstein et al., JNCI 1998; Goldstein et al., CEBPT 2000; Goldstein et al., JNCI 2000



Evolution of Dysplastic Nevus

Tucker et al. Cancer 2002

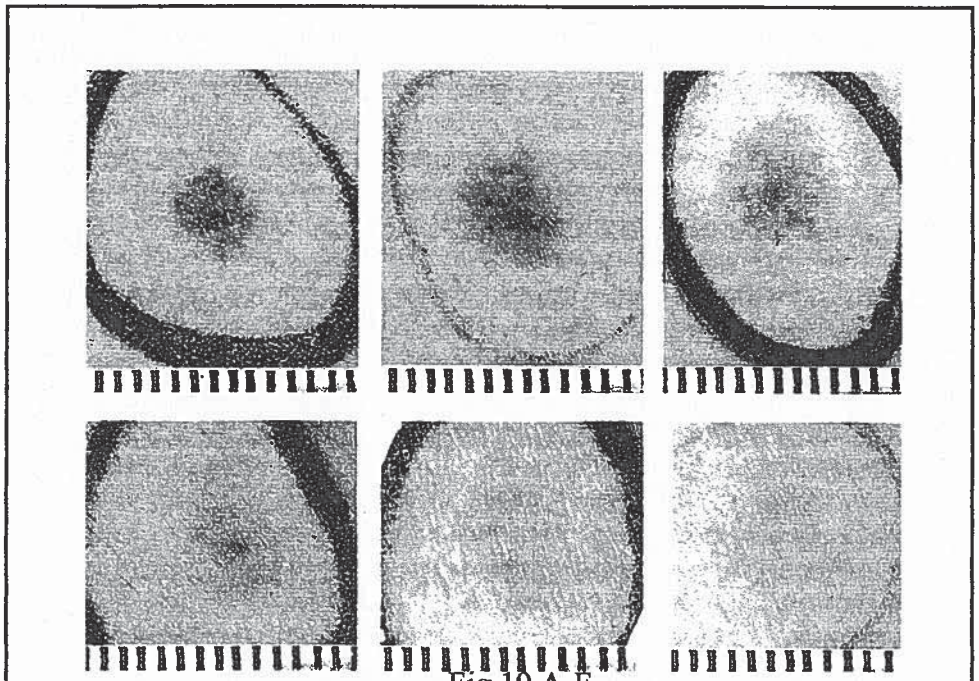
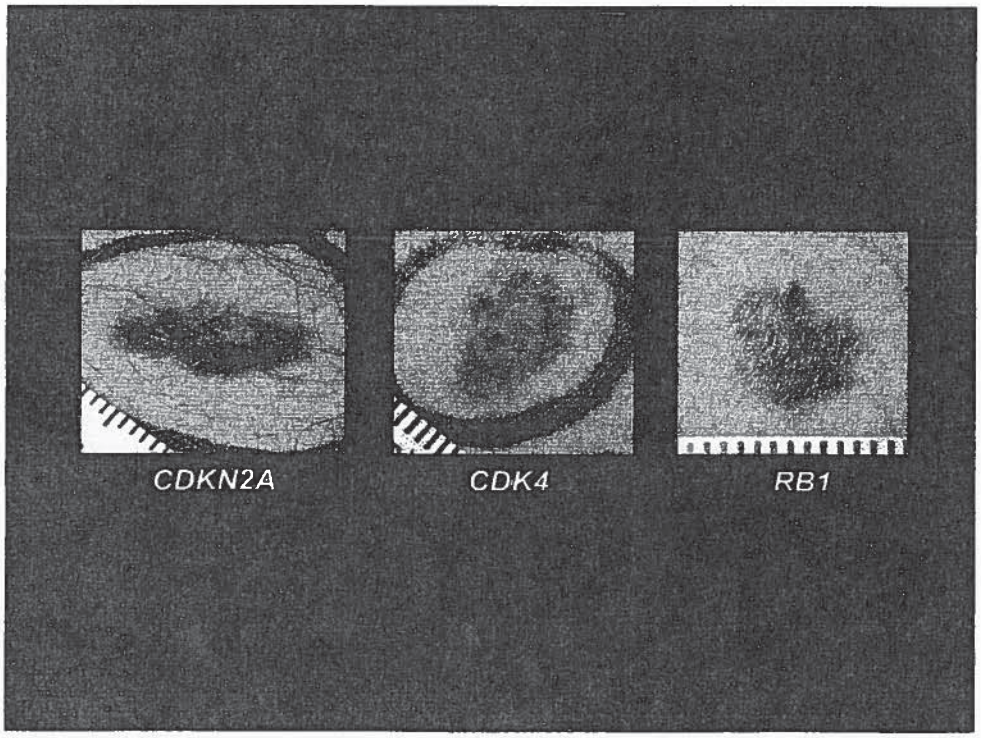


Fig 19 A-F
Involuting dysplastic nevus

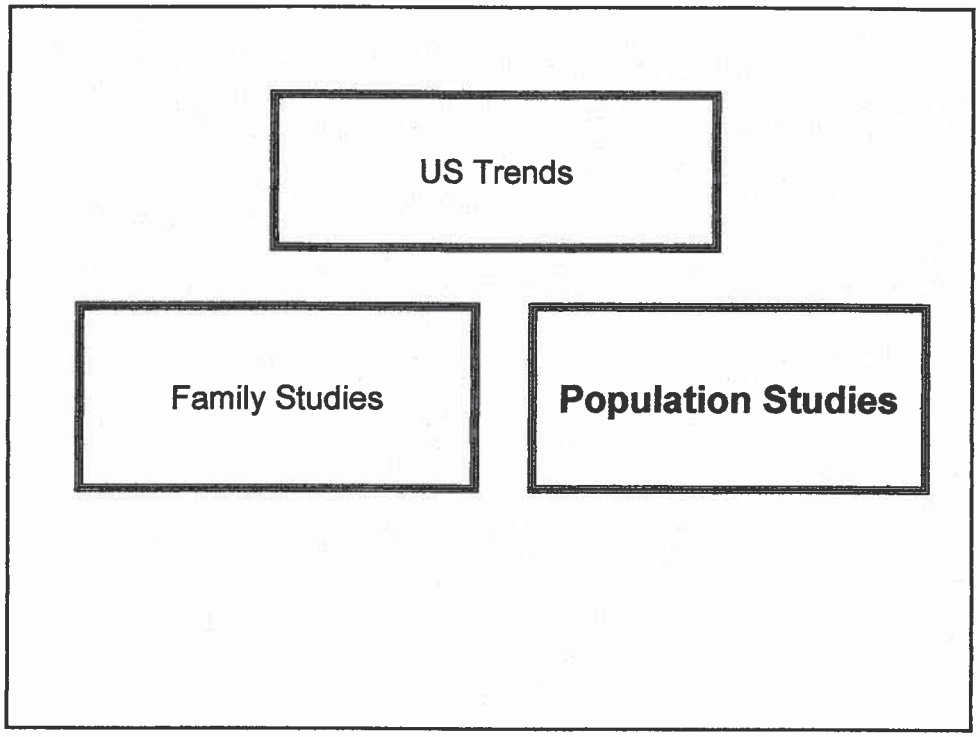


Clinical Guidelines for High Risk Families

- Avoidance of midday sun and use of sun protective measures
- Monthly self examination
- Routine health care worker examinations
- Biopsy of lesions only if changing in manner worrisome for melanoma

Average Thickness of Prospective Melanomas

T Stage	*CDKN2A* (#)	*CDK4* (#)	Unknown (#)
T1a	0.34 (52)	0.24 (13)	0.36 (7)
T1b	0.59 (4)		0.68 (2)
T2a	1.45 (4)	1.13 (1)	
T3a	2.10 (1)		
Unk	(2)		



Melanoma Case-Control Study

- Evaluate the role of dysplastic nevi and common nevi in melanoma risk outside of high risk families
- Develop better sun exposure measures
  - Age at exposure
  - Types of exposure
- Collaborative study with University of Pennsylvania and UCSF

Host Factors in Melanoma

Characteristic	Relative Risk	Percent of Cases
Dysplastic nevi	2-20+	50
>25 Ordinary nevi	2-4	16
Light complexion	1.7	64
Freckling	2-4	50
Sunburn	1.5	75
Solar damage	3	6

Tucker et al., JAMA, 1997; also in prep

Sun Exposure

- Blistering sunburns at different ages
- Hours outdoors during different ages
- Full life residential history to develop measure of average annual UVB intensity

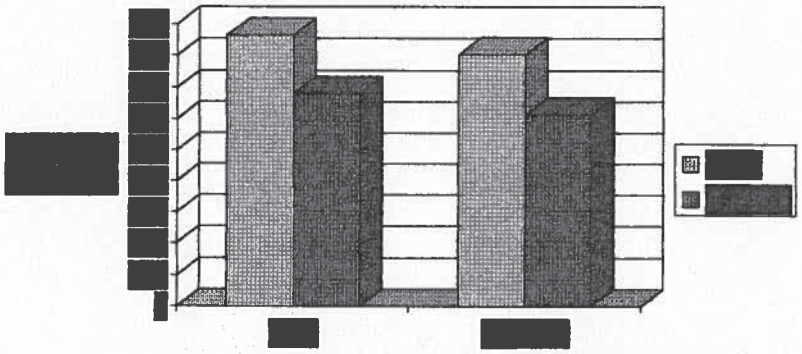
Average Annual Intensity of UVB

- First individual dose estimate based on residence
- Consistent increase in risk with exposure
- Between Atlanta and New Orleans
  - 38% increase in melanoma risk in men
  - 32% increase in melanoma risk in women
- No age at exposure effects

Fears et al., Cancer Res., 2002

Is there a healthy tan?

Yearly Hours Outdoors as Adults Among Deep Tanners



US Trends

Family Studies

Population Studies

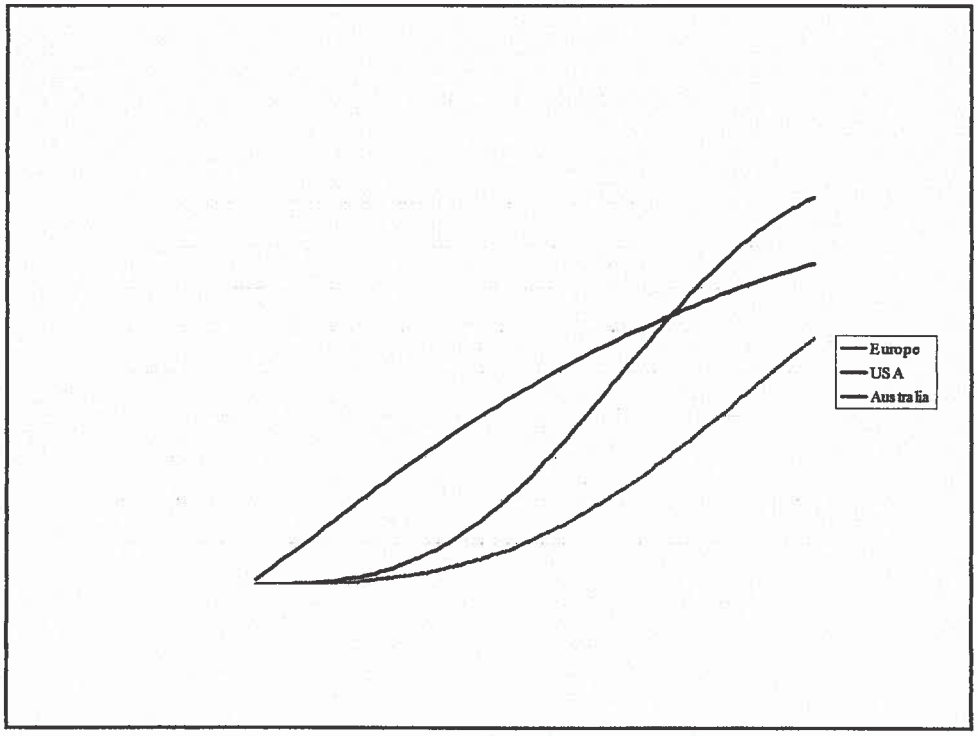
Melanoma Genetics Consortium

- Established in 1997
- Currently 16 groups studying high risk families are members
- Goals
  - To identify additional melanoma susceptibility genes
  - To evaluate penetrance of identified genes
  - To identify other modifiers of risk

Penetrance of CDKN2A Mutations

- Melanoma Genetics Consortium
- 80 families with documented *CDKN2A* mutations from Europe, Australia, U.S.
- Logistic regression model with survival
  - Gender
  - p14ARF alterations
  - Population melanoma incidence rates

Bishop et al., JNCI, 2002.



Genetic Testing for *CDKN2A* Mutations

- Based on penetrance findings, reassessed recommendations
- Generally premature to offer *CDKN2A* testing
  - Likelihood of finding mutation low
  - Penetrance highly variable
  - Does not change recommended clinical care for family members already in place

Kefford et al., Lancet, 2002

Summary

- Described melanoma trends in U.S. population
- Clinically investigated high risk families
- Conducted population studies to evaluate risk factors
- Created consortium to identify new genes and modifiers of risk

Collaborators

- Alisa Goldstein
- Mary Fraser
- Patricia Hartge
- Thomas Fears
- Jeffery Struewing
- Maria Teresa Landi
- Ahmedin Jemal
- Susan Devesa
- Wallace Clark
- David Elder
- Dupont Guerry
- Elizabeth Holly
- Richard Sagebiel
- Allan Halpern
- Melanoma Genetics Consortium