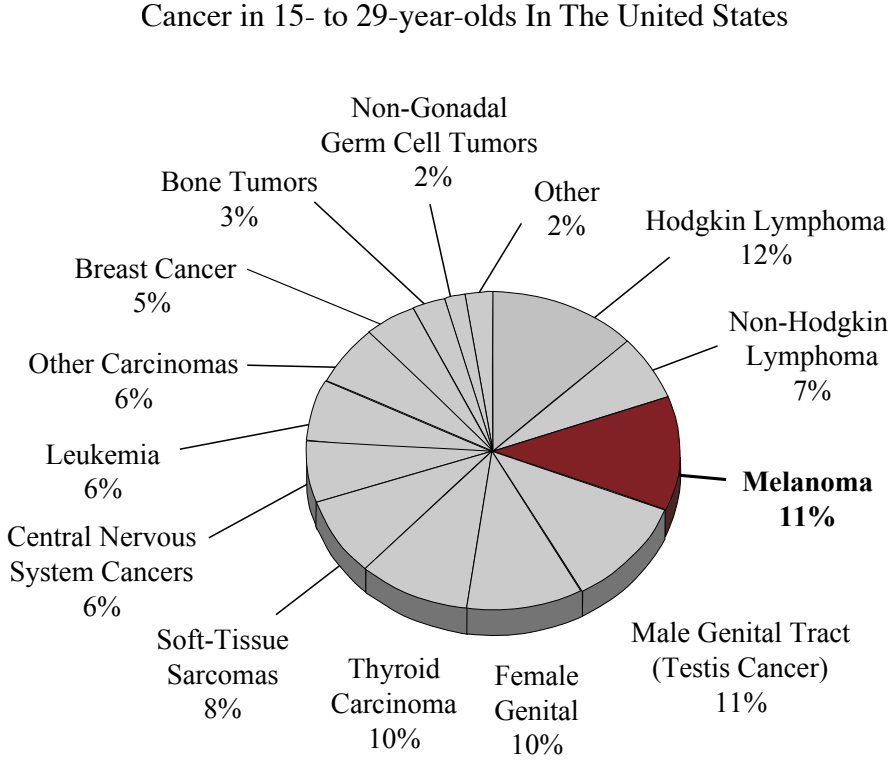
Chapter 5

Malignant Melanoma



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HIGHLIGHTS

Incidence

- Melanoma accounted for 11% of all malignant neoplasms in individuals 15 to 29 years of age in the time period 1975 to 2000, and was the 2nd most common type of cancer in this age group. An estimated 2,600 individuals 15 to 29 years of age were diagnosed with malignant melanoma in the U.S. during the year 2000.
- As a proportion of all cancer, malignant melanoma peaked at 25 to 29 years of age, accounting for 12.8% of all cancers in this age group.
- The incidence of melanoma increased over time in individuals 15 to 29 years of age, but not as rapidly as the dramatic increase observed in older adults.
- Up to age 40, females had a higher incidence of melanoma than males, with a peak ratio of 1.8:1 (female:male) occurring between 20 and 24 years of age.
- After age 40 the gender incidence predominance reverses; older men had twice the incidence of older females.
- White, non-Hispanic individuals at any given age had a far higher incidence of malignant melanoma than any other race or ethnicity, including non-white Hispanic individuals. 90% of all melanomas diagnosed in the U.S occurred in white, non-Hispanic individuals.
- For other races/ethnicities, a greater proportion of melanoma cases occurred at younger ages than at older ages.
- The relative incidence of melanoma among races/ethnicities in the U.S. was inversely correlated with skin pigmentation. The order of incidence, from highest to lowest, was white non-Hispanics, Hispanics, Asians/Pacific Islanders, and African Americans.
- Among 15- to 29-year-olds, the increase in incidence of malignant melanoma occurred primarily in females; the trunk was the most common anatomic location.
- Head and neck melanomas were distinctly uncommon in 15- to 29-year-olds, in contradistinction to older adults.

Mortality and Survival

- As expected from the incidence patterns, the vast majority of deaths from melanoma among adolescents and young adults occurred in white, non-Hispanic patients.
- Mortality for malignant melanoma showed continued improvement over time in all age groups, but particularly in 20- to 29-year-olds.
- Melanoma in 10- to 39-year-olds was highly curable, with 5-year survival rates exceeding 90%.
- Females had a higher survival rate—exceeding 95% at five years among 15- to 29-year-olds—in comparison to males, who had an 88% 5-year survival rate during the past quarter century.
- Males with malignant melanoma of the head and neck had the worst survival rate, determined to be 80% at five years during the past quarter century.
- In the interval from 1975 to 1999, males had a greater survival improvement than females, however—particularly in the 15- to 24-year age group.

Risk Factors

- The etiology of melanoma in 15- to 29-year old individuals is not known.
- Solar/ultraviolet irradiation does not appear to be as important a causative factor in this age group as it is in older individuals.
- An exception may be those melanomas that arise in the skin of the trunk, where most of the increase has occurred, particularly in females. The increase at this body site may be a result of cultural changes that have resulted in more incidental and deliberate skin exposure (sun tanning) to this part of the body.
- Mutations in CDKN2A and CKD4 explain some of the familial melanomas, but the proportion of these mutations that occur in melanomas in 15- to 29-year-olds is not established.

INTRODUCTION

Melanoma was one of the most frequent cancers in adolescents and young adults in the period 1975 to 2000—second in incidence only to lymphoma—and accounted for one in nine patients with cancer in 15- to 29-year-olds. In the year 2000, approximately 2,600 individuals were diagnosed with melanoma in the adolescent and young adult age group (Table 5.1); this number has likely increased in light of population growth and the rising incidence of melanoma (see *Trends in Incidence*).

METHODS, CLASSIFICATION SYSTEM AND BIOLOGICAL IMPLICATIONS

Malignant melanoma is classified in the International Classification of Childhood Cancer (ICCC) in category XI(d) as one of the *Carcinomas and Other Epithelial Neoplasms* (category XI). The ICCC melanoma category specifies that malignant melanoma includes categories 8720-8780 (*Nevi and Melanomas*) in the International Classification of Diseases for Oncology (ICD-O-2). These categories include malignant melanomas (8720-8721, 8722-8723, 8730, 8740, 8742-8745, 8761, 8770-8774), malignant melanoma in Hutchinson melanotic freckle (8742), and malignant melanoma in precancerous melanosis (8741). ICD-O-3 histologies meningeal melanomatosis (8728) and mucosal lentiginous melanoma (8746), were also included.

One biologic implication of the classification is that the ICCC category of "malignant melanoma" does not include benign lesions (nevi and other precancerous histologies), which do occur in this age group. The SEER site recode for melanoma is limited to malignant melanomas of the skin. In the ICCC, malignant melanoma refers to malignant melanoma of all sites in the body (ICD-O Topography codes C00.0-C80.9). ICD-O allows the melanomas to be further classified by the site of origin. For the 25- to 29-year age group, the sites where most melanomas occurred were skin (further subdivided into skin location: head/neck, upper limb/shoulder, trunk, lower limb/hip), genital tract (included with pelvis), and eye (included with head/neck).

As explained in the *Methods* chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

INCIDENCE

Age-Specific Incidence

The incidence of melanoma increased with age throughout the lifespan (Figure 5.1). Melanoma was exceedingly rare in prepubertal patients, accounting for only 1% of the cancers seen in patients under age 15. Considering males and females together, the incidence of melanoma increased from age 20 to 80 at a remarkably linear rate (data not shown). When males and females are evaluated separately however, the patterns are not linear (see *Gender-Specific Incidence*), with a switch in gender dominance occurring at about age 40. As a proportion of all cancers, the incidence of melanoma peaks between 20 and 40 years of age and then decreases. It accounts for 7.1% of all cancers diagnosed in 15- to 19-year olds, 12.0% of the cancers in the 20- to 24-year age group, and 12.8% of cancer in 25- to 29-year olds (Figure 5.1). From 1975 to 2000 there were about 80,000 cases of melanoma reported in the SEER population base, with 7.6% occurring in patients aged 15 to 29 years. Melanoma accounted for 11.5% of all cancers seen in this age group.

Table 5.1: *Incidence of Melanoma in Persons Younger Than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
Average incidence per million, 1975-2000, SEER	0.7	0.9	2.8	14.0	38.9	69.4
Average annual % change in incidence, 1975-2000, SEER	na	na	na	0.87	1.23	0.58
Estimated incidence per million, year 2000, U.S.	na	na	4.0	15.5	44.4	73.8
Estimated number of persons diagnosed, year 2000, U.S.	13	19	81	314	841	1431

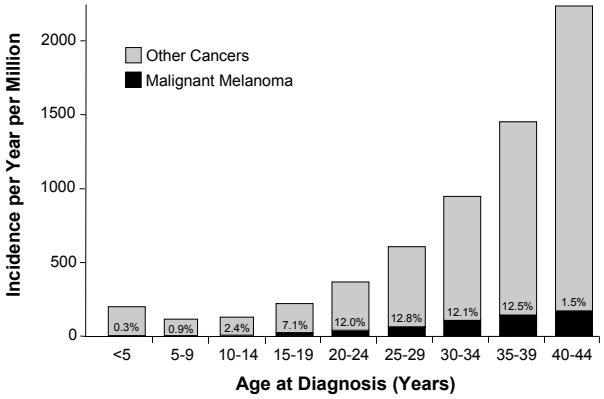

Figure 5.1: Incidence of Malignant Melanoma Relative to All Cancer, SEER 1975-2000

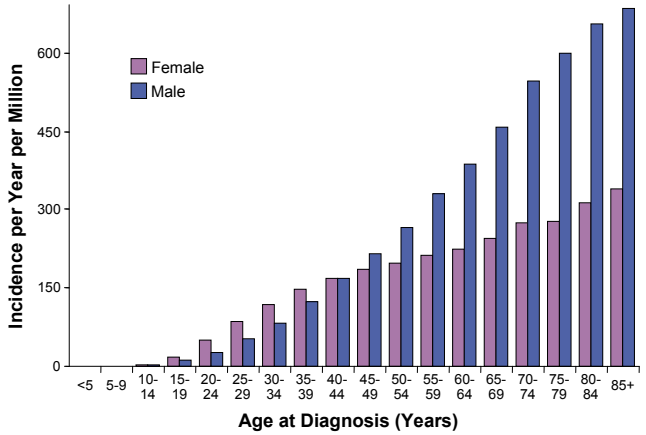

Figure 5.2: Incidence of Malignant Melanoma by Gender, SEER 1975-2000

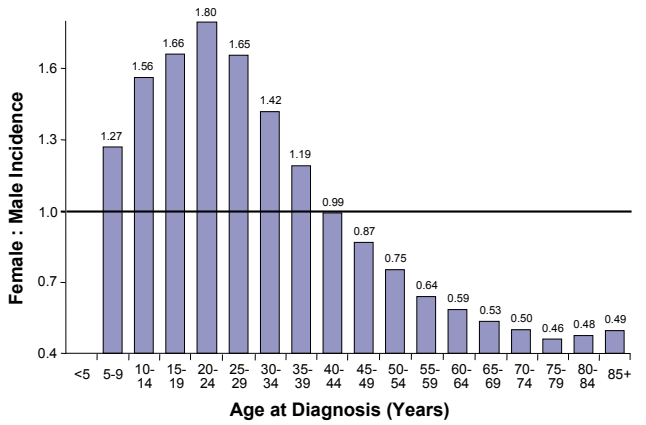

Figure 5.3: Female : Male Incidence Ratio, Malignant Melanoma, SEER 1975-2000

Gender-Specific Incidence

In females, the incidence increase was triphasic, with a rapid increase between 20 and 40 years of age, a slower increase from 40 to 70 years of age, and then an accelerated increase thereafter that was not as rapid as the increase in young adults (Figure 5.2). In males, the temporal pattern was sigmoid, with a slower increase in 20- to 40-year-olds than in females and the most rapid increase between 50 and 80 years of age. Below age 40, the incidence in females was higher in all age subgroups than in males (Figure 5.2). In terms of relative gender incidence, the female predominance peaked sharply between 20 and 25 years of age, at a ratio of 1.8 (Figure 5.3). The gender predilection switched by age 40 years, after which males were at substantially higher risk than females. By age 70, males developed melanoma at twice the rate of females (Figure 5.3).

Site-Specific and Gender Differences in Incidence

In 15- to 29-year olds, melanoma occurred most commonly on the trunk and legs, and least commonly on the head and neck (Figure 5.4). In older persons, the trunk was the least likely site of presentation, whereas head and neck incidence dramatically increased, becoming the most common site (Figures 5.5 and 5.6). In 15- to 29-year-old

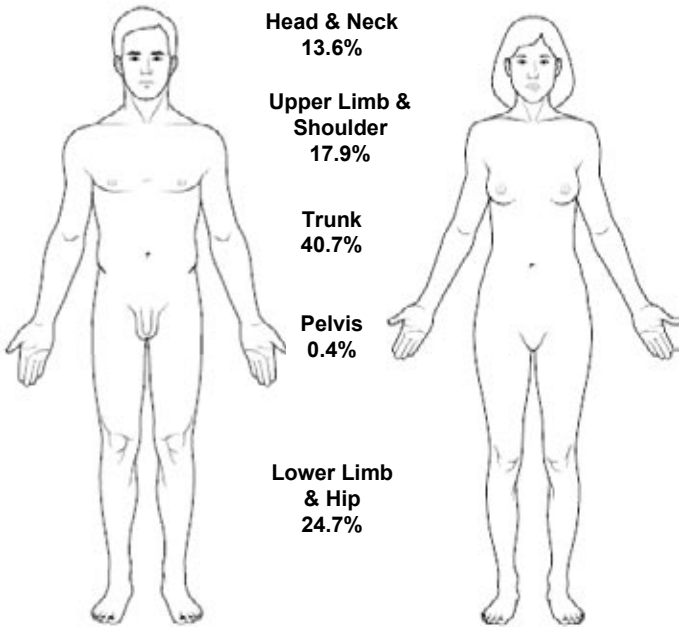

Figure 5.4: Common Sites of Malignant Melanoma in 15- to 29-Year-Olds, SEER 1992-2002. Drawings by Medscape

males, the majority of melanomas occurred on the trunk (Figure 5.5), which remained the most frequent anatomic site until age 80, when—as in females—head and neck sites rapidly increased and became the most common site (Figure 5.6). The extremities were much more likely to be affected in females than in males, and females were more likely to have melanoma arising in the legs than in the arms (Figures 5.5 and 5.6).

Racial/Ethnic Differences in Incidence

In the U.S., as in most countries for which comparable data are available, the incidence of melanoma was highest in fair-skinned persons (Figure 5.7). The proportion of non-white persons developing melanoma was inversely proportional to age throughout the life span, decreasing from 15% during childhood to < 5% by age 70 (Figure 5.8). This complements the age-related increase in the incidence of melanoma among whites. Among 15- to 29-year-olds, 90% of the patients with melanoma were white non-Hispanics. The relative incidence of melanoma among races/ethnicities in the U.S. was proportional to skin pigmentation, with the order of incidence decreasing from white non-Hispanics to Hispanics, Asians/Pacific Islanders, and African Americans/blacks.

Incidence Trends

The increasing incidence of melanoma during the past generation has been well established. However, this increase occurred predominantly in older adults—the older the age group, the greater the increase (Figure 5.9). The increase in 15- to 29-year-olds was insignificant for males and for both males and females younger than age 15 (Figures 5.10 and 5.11). Over age 30, the increase was statistically significant for both males and females, and at all anatomic skin sites (trunk, upper extremity, lower extremity, and head/neck).

Among females 15 to 29 years of age, the increase was statistically significant for the trunk, lower extremities and head/neck, but not for the upper extremities (Figure 5.11). The greatest increase among 15- to 29-year-olds occurred at truncal sites in females.

Among males 15 to 29 years of age, there was no comparable increase at any site (Figure 5.12). Only in men over 30 years of age were there statistically significant

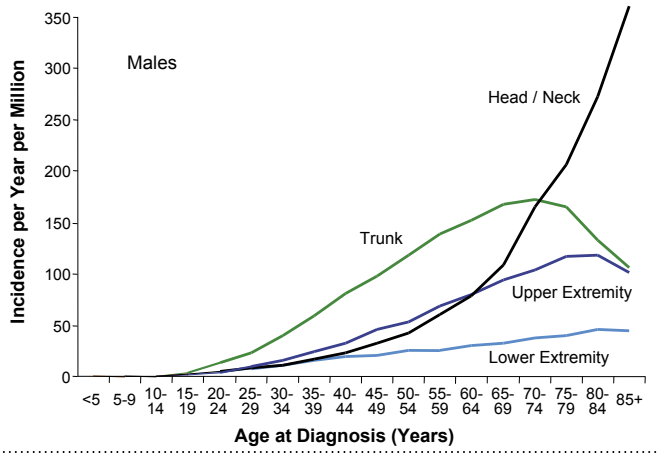

Figure 5.5: Incidence of Malignant Melanoma by Body Site for Males, SEER 1975-2000

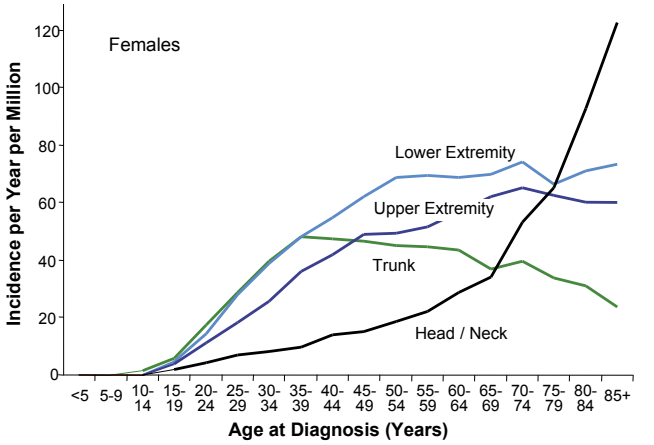

Figure 5.6: Incidence of Malignant Melanoma by Body Site for Females, SEER 1975-2000

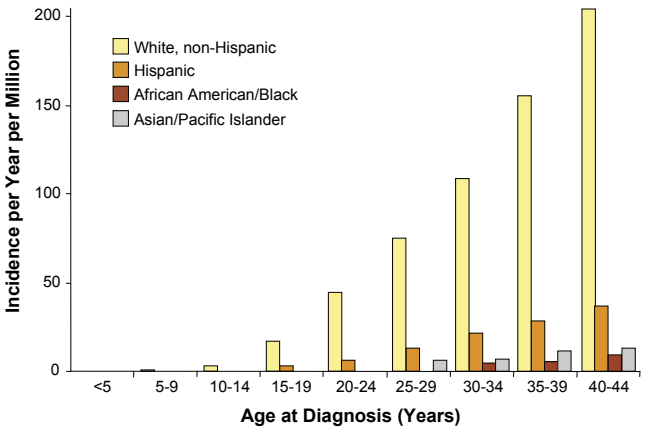

Figure 5.7: Incidence of Malignant Melanoma by Race/Ethnicity, SEER 1990-2000

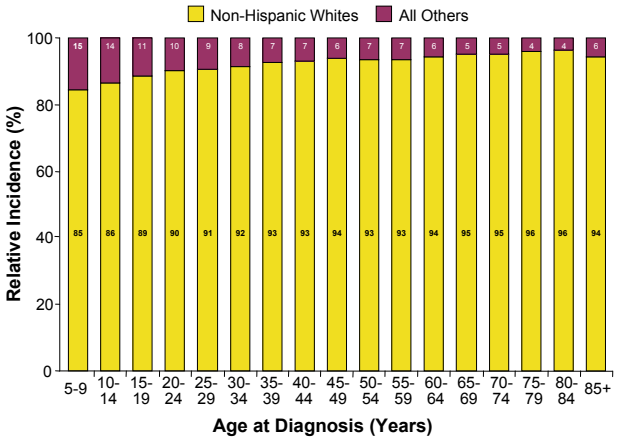

Figure 5.8: Relative Incidence of Melanoma in Non-Hispanic Whites, SEER 1990-2000

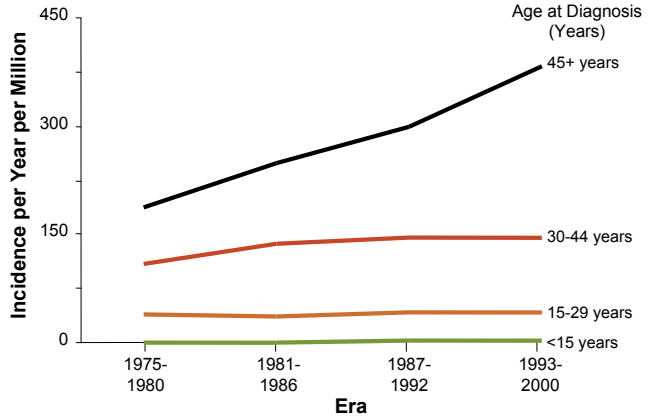

Figure 5.9: Incidence of Malignant Melanoma by Era, All Sites, SEER 1975-2000

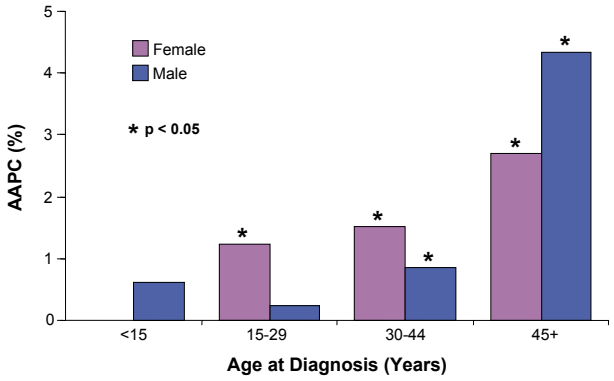

Figure 5.10: Average Annual Percent Change (AAPC) in Incidence for Malignant Melanoma by Gender, SEER 1975-2000

increases in incidence. The greatest increase in 30- to 44-year-old males was in the lower extremities.

In females, the greatest increase occurred at truncal sites, with the increase in 30- to 44 year-olds matching that which occurred above age 45 (Figure 5.13).

OUTCOME

Mortality

The U.S. death rate for melanoma among individuals younger than age 45 decreased steadily from 1975 to 2000 (Figure 5.14).

In patients younger than 45 years of age, males had a higher mortality rate than females, despite the fact that melanoma incidence was higher in females under age 40 (Figure 5.15).

Concordant with the incidence pattern, the vast majority of deaths from melanoma in the U.S. were in white non-Hispanic patients (Figure 5.16).

Those in the 20- to 29-year age group experienced the greatest reduction in mortality during the period 1975 to 2000 (Figure 5.17). Mortality reduction in this age group continued in the most recent decade (1990 to 2000) at a rate similar to that of the past quarter century (1975 to 2000), but was not as dramatic as the reduction in national mortality for melanoma among 30- to 44-year-olds (Figure 5.18).

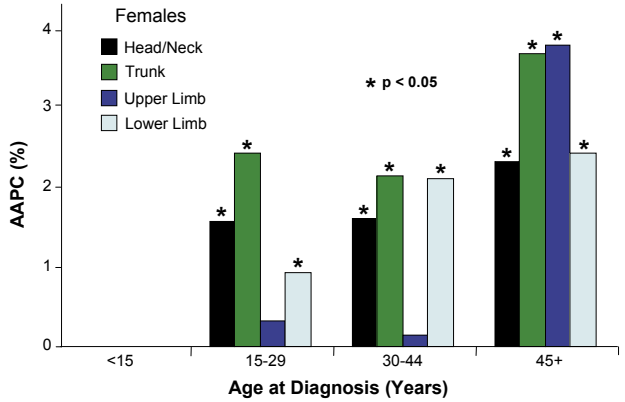

Figure 5.11: Average Annual Percent Change (AAPC) in Incidence for Malignant Melanoma in Females by Body Site, SEER 1975-2000

Survival

During the past quarter century, survival rates averaged 90% among patients diagnosed with melanoma before 45 years of age (Figure 5.19). The youngest (less than 5 years of age) and oldest (40 to 44 years old) in this age range had lower 5-year survival rates than patients in the other age groups (Figure 5.19).

In patients younger than 45 years of age, males had a lower 5-year survival rate than females in all age groups (Figure 5.20). This difference is particularly obvious in patients younger than 30 years of age. Among 15- to 29-year-olds, males with head and neck tumors had a lower 5-year survival rate than males with tumors at other anatomic locations (Figure 5.21).

Survival Trends

Survival rates in patients of all age groups with melanoma improved during the period 1975 to 1999 (Figure 5.22). The improvement was least apparent in children and adolescents younger than 15 years of age, although the low incidence of melanoma in this age group made it difficult to discern such a change.

Young males had a greater rate of survival improvement in the period 1975 to 1999 than females, particularly among 15- to 24-year-olds (Figure 5.23).

RISK FACTORS

The etiology of melanoma is not completely understood, although a variety of epidemiological studies have iden-

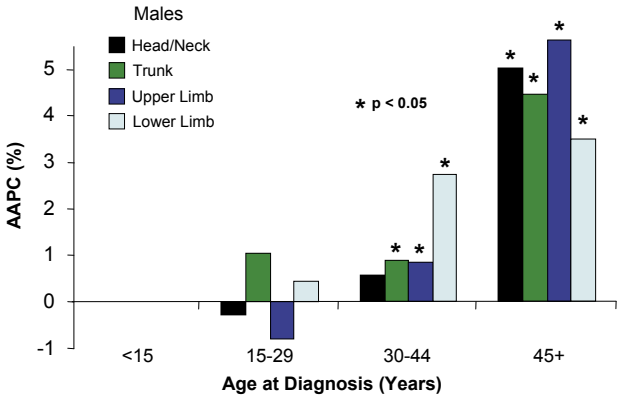

Figure 5.12: Average Annual Percent Change (AAPC) in Incidence for Malignant Melanoma in Males by Body Site, SEER 1975-2000

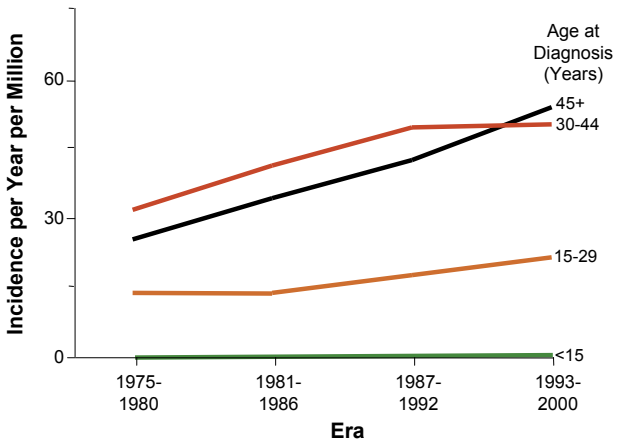

Figure 5.13: Incidence of Truncal Malignant Melanoma in Females by Era, SEER 1975-2000

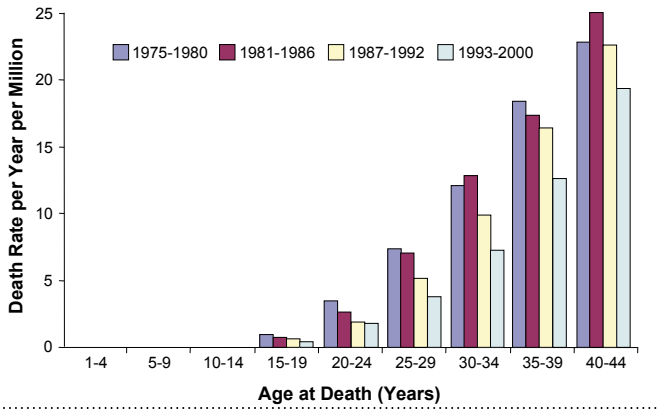

Figure 5.14: National Mortality for Malignant Melanoma by Era, U.S.

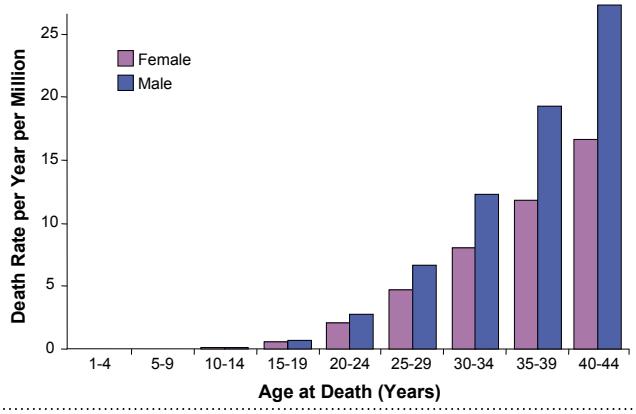

Figure 5.15: National Mortality Rate for Malignant Melanoma by Gender, U.S., 1975-2000

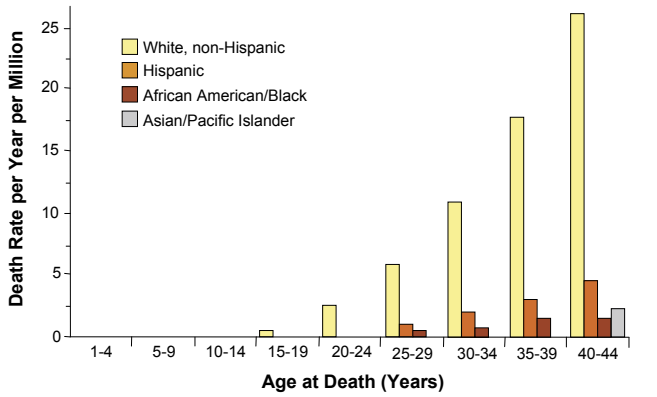

Figure 5.16: Cancer Mortality for Melanoma by Race/Ethnicity, U.S., 1990-2000

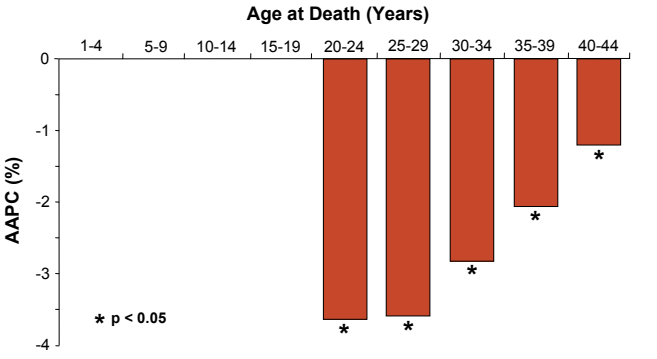

Figure 5.17: Average Annual Percent Change (AAPC) in National Mortality for Malignant Melanoma, 1975-2000

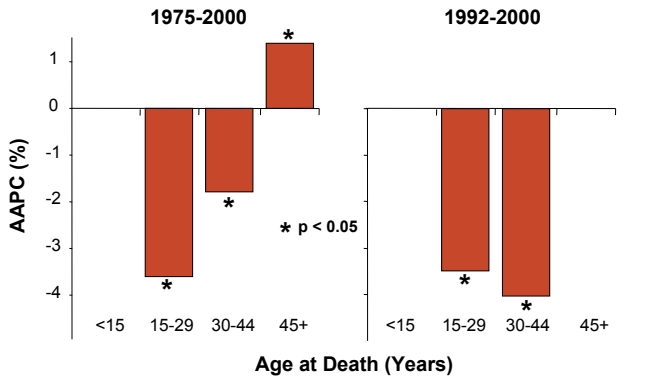

Figure 5.18: Average Annual Percent Change (AAPC) in National Mortality for Malignant Melanoma

tified several factors associated with an increased risk of developing this disease (Table 5.2).[1]

Some melanoma risk factors are age-dependent. For example, rare congenital and infantile melanomas (melanoma seen from birth to one year of age) may be the result of transplacental transmission or originate in a medium- or large/giant-sized congenital nevus.[2] Six cases of transplacental transmission of melanoma affecting a fetus have been reported, and only one of these patients survived long-term.[3] For patients with a large congenital nevus, the estimated lifetime risk of developing melanoma is less than 5%.[4] Over 80% of these patients have nevi located in the head and trunk area, and the melanoma that develops in these lesions usually develops before the age of 10.[4] Curiously, some of the melanomas seen in these patients arise in extracutaneous sites.[4] Other conditions associated with the development of melanoma in the first two decades of life include xeroderma pigmentosum, neurocutaneous melanosis, and immunosuppression.[5]

Females have a higher percentage of melanomas that occur in the upper or lower extremities, and as a result may be diagnosed earlier, with a resultant more favorable stage and prognosis. In males, the predominant site

Table 5.2: *Risk Factors Associated with the Development of Cutaneous Melanoma*[1]

RISK FACTOR	RELATIVE RISK
Immunosuppression	2-8
Excessive sun exposure	3-5
Sun sensitivity	2-3
White race	12
Lentigo maligna	10
Increased number of nevi	2-64
Older age (> 15 years)	88
Clinically atypical moles (with history of familial melanoma)	148
Clinically atypical moles (without a family history of melanoma)	7-70
Previous diagnosis of melanoma	5-9
Cutaneous melanoma in parents, children, siblings	2-8

is the trunk, which may result in a delayed diagnosis since these lesions are least likely to come under scrutiny. These gender-related patterns may explain why males with melanoma have had a lower survival rate than females.

Genetic susceptibility

Family history of melanoma (one or more first-degree relatives affected with melanoma) has been reported to occur in up to 12% of cases of melanoma.[6] Mutations in the CDKN2A and CDK4 genes account for 20%-25% of cases of high-risk melanoma families. The likelihood of finding a mutation in the CDKN2A gene correlates with the number of affected family members, and ranges from 5% in families with two affected individuals to 40% in those with three or more affected members.

Solar Exposure

Approximately half of all cases of melanoma worldwide have been attributed to sun exposure. Table 5.3 shows the results of a review of case-controlled studies that have investigated the relationship between sun exposure and melanoma.[7]

Nevus phenotype

Increased numbers of benign melanocytic nevi have been consistently associated with an increased risk of developing melanoma. In a study from Queensland Australia, the strongest risk factor associated with the development of melanoma in 15- to 19-year-olds was the presence of more than 100 nevi greater than 2 mm in diameter.[8] The presence of dysplastic or clinically atypical nevi confers an increased risk of melanoma. In the familial setting, the majority of melanomas have been reported to arise from dysplastic nevi.[9]

Table 5.3: *Odds Ratio of Developing Melanoma According to Type of Sun Exposure*[7]

TYPE OF EXPOSURE	ODDS RATIO (95% CL)
Intermittent	1.87 (1.67-2.09)
Occupational	0.76 (0.68-0.86)
Total	1.2 (0-1.44)
Sunburn	
Adult/lifetime	1.91 (1.69-2.17)
Adolescence	1.95 (1.6-2.36)
Childhood	1.63 (1.35-1.95)

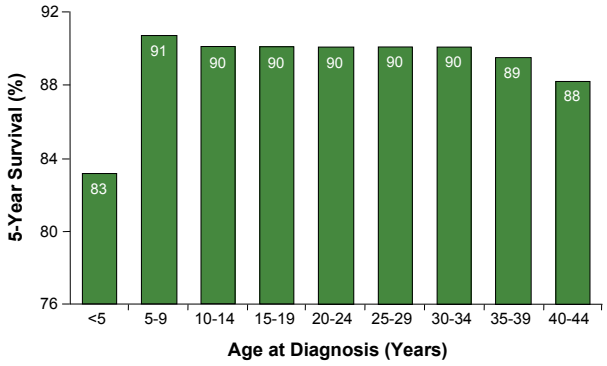

Figure 5.19: 5-year Survival Rate for Malignant Melanoma, SEER 1975-1999

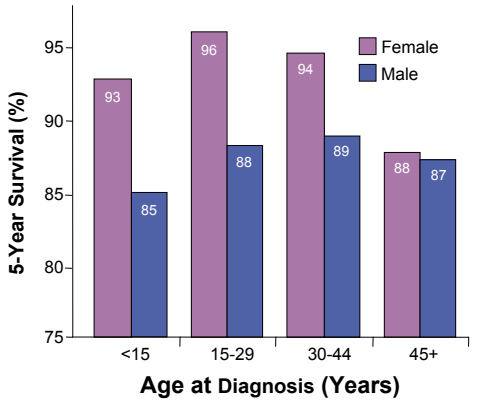

Figure 5.20: 5-year Survival Rate for Malignant Melanoma by Gender, SEER 1975-1999

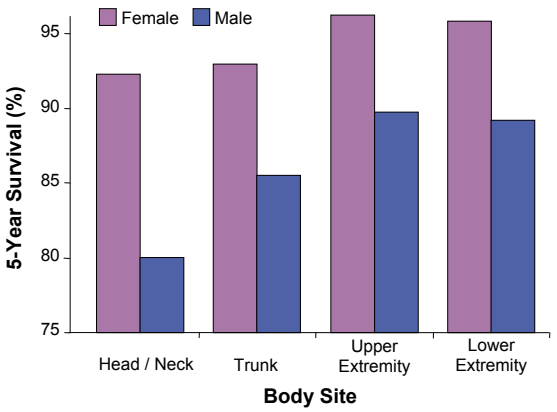

Figure 5.21: 5-year Survival Rate for Malignant Melanoma by Gender and Body Site for 15- to 29-Year-Olds, SEER 1975-1999

SUMMARY

Melanoma is a frequent, generally curable cancer of older adolescents and young adults that peaked in female predominance in the 15- to 29-year age group and shifted to male predominance by age 40. This gender predilection crossover suggests that the etiology and pathogenesis of melanoma is different in females and males, and that it differs for young adults and older adolescents as compared to older adults. Females were more likely to sustain melanoma early in life, while males were twice as likely to develop this neoplasm after age 60. Given the many years that most environmental exposures require to induce cancer, the gender reversal implies that for adolescent and young adult females, the events leading to carcinogenesis began during childhood and were different etiologically than those for males. If solar/ultraviolet exposure was a major cause of melanoma in young adults, the latency would not be expected to lead to a peak incidence during early adult life, or to be shorter in females than in males. Thus, solar radiation as the sole risk factor is not consistent with the age- and gender-specific incidence patterns seen in adolescents and young adults.

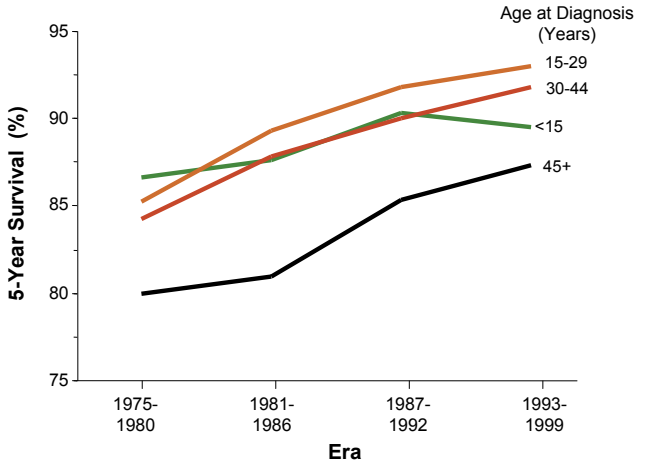

Figure 5.22: 5-Year Survival Rate for Malignant Melanoma by Era, SEER

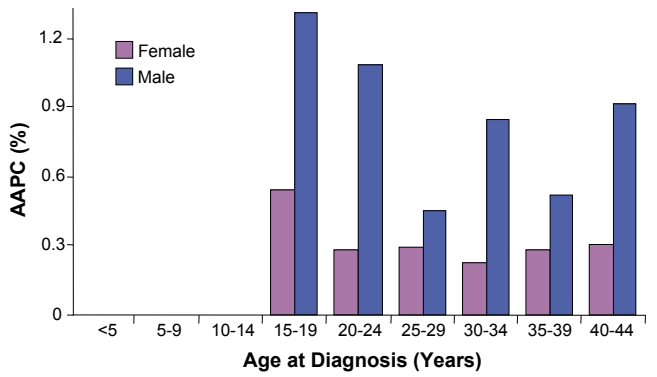

Figure 5.23: Average Annual Percent Change (AAPC) in 5-Year Survival Rate for Malignant Melanoma by Gender, SEER 1975-1999

Melanoma in young adults steadily increased in incidence, particularly in females, but at slower rates than observed in older adults. For males and females over the age of 30, this increased incidence over the past quarter century was statistically significant, and occurred at all major sites in the body (head/neck, trunk, arms, legs). For those 15 to 29 years of age, only females showed a significant increase in incidence, which was limited to certain sites—most notably the trunk and lower extremity.

Whereas the increasing incidence in older adults has been strongly correlated with solar and other forms of ultraviolet light exposure, there has been no direct evidence that melanoma in children, adolescents, and young adults is related to these factors. On the contrary, most of the melanomas that occur in young persons arise in dysplastic nevi or in parts of the body that are likely to have been protected from ultraviolet light exposure (e.g. trunk and head/neck).

On the other hand, the observed increased incidence among 15- to 29-year-olds—primarily in females, and specifically on their trunks—is compatible with a solar etiology that manifests skin-related cancer this early in life. The cultural emphasis on suntans and increased skin exposure—particularly that of the trunk in females—may well account for this epidemiologic dynamic (the *bikini effect*). If so, this may be the first evidence that ultraviolet exposure can cause melanoma within a limited number of years, rather than over a decade or more, as previously thought.

The greater susceptibility of fair-skinned individuals to melanoma is a long-standing finding that has been doc-

umented in this report to occur at all ages. That people of non-white race and/or ethnicity have a greater relative incidence of melanoma during childhood, adolescence and early adulthood is compatible with the premise that non-environmental factors are primarily responsible for melanoma development during early life. Solar/ultraviolet exposure either is more causative in later life and/or takes many years of exposure to result in melanoma. The age at which the switchover in the etiologies occurs—from non-environmental to solar exposure—cannot be determined from these data, but it seems reasonable to predict that it occurs between 20 and 40 years of age.

That young adult females are frequently diagnosed with a more favorable stage and prognosis than are men appears to be related to the site of development. In females, the most common site is an extremity, whereas in males the predominant location is the trunk. This gender-related pattern may explain why males with melanoma have had a lower survival rate than females.

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