

## Malignant melanoma in Bari. Epidemiological data.

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### Summary

Epidemiological data regarding 1,504 cases of primary malignant melanoma of the skin removed and diagnosed in Bari from 1975 to 2000 are reported. Particularly, besides the total number of cases, figures per year, sex, age and site of the primary tumor are reported. The prevalence of melanoma is increasing even in Bari of about 10% per year. Females (55%) are affected slightly more frequently than males. With regard to the age, the most affected five-year period is between 56 and 60, with 75% of cases included between 36 and 75 years. Three cases of prepubertal melanoma with a prevalence of 0.2% of the cases are reported. Particular attention was paid to the different distribution per site according to the sex. Once confirmed the more frequent involvement of the lower limb in females and of the trunk in males, we subdivided in age groups the cases of melanoma. We showed that this different localization in the two sexes starts after 30 years and persists after 60 years. As the more frequent localization on the lower limb in the female lacks in the 16-30 age group and on the other hand is present in the over sixty age group, the involvement of this site is probably not exclusively related to sex-linked hormonal factors.

### Key words

Melanoma, sex in melanoma, skin favorite sites in melanoma.

**A**s the prevalence of melanoma is continuously increasing throughout the world (3), we decided to verify in a retrospective study whether or not in Bari (Italy) the prevalence of this malignancy changed in the period 1975-2000. We wanted also verify in this preliminary report the distribution according to the age, sex and site involved of our population affected by melanoma. Particularly, we tried to understand the factors responsible for the different predilection of site in the two sexes. As a matter of fact, most Authors underline the more frequent localization on the trunk, particularly on the back, in males and on the lower limb in females. However, the factors responsible for this different predilection are not yet elucidated.

### Material and methods

The actual series reports 1,458 cases of primary melanoma of the skin diagnosed and removed in Bari from 1975 to 2000. Thus 201 cases with metastases at the moment of diagnoses were ruled out. Even two cases lacking sex and age and 48 cases -23 females and 25 males- lacking the age were ruled out.

From 1975 to 1991 are reported only the cases removed in the University Hospital and from 1992 are also reported the cases of the regional Hospital "Di Venere". The cases of melanoma significantly increased in the latter hospital from 1994, due to the transfer in this hospital of one of us (L.M.). Our population

consists of 648 males and 810 females ranging in age between 3 and 98 years.

*Cases of melanoma in subjects aged less than 13 years.* The youngest subject (D.A.P.), aged 3 years was hospitalised in a Department of Plastic Surgery of the University Hospital in 1975, due to a local recurrence of a pigmented lesion, which had been removed two months before in a hospital of the Bari province. The child after removal had already undergone radiotherapy. A few days after the hospitalisation, metastases appeared on the right lower limb along with a gross enlargement of the right inguinal lymph nodes. Six months later the child died at home due to diffuse metastases.

In 1996 a child, who was born on 1990, August, 18, affected by xeroderma pigmentosum, was hospitalised in the “Di Venere” hospital. From an indeterminate period of time he presented a superficial melanoma on the dorsum of the nose, 2 x 2 centimeters in size, and a basocellular carcinoma on the naso-orbital groove. The pathological findings led to diagnose an in situ, superficial spreading melanoma with elastosis and foci of acantholytic dyskeratosis.

In 1998 a child, who was born on 1990, October, 20 was hospitalised in the “Di Venere” Hospital due to a pigmented, ulcerated, nodular melanoma, 2.5 centimeters in size. The pathological findings led to diagnose nodular malignant melanoma, IV Clark, 2.8 millimeters.

The significance level  $\alpha = 0.05$  was chosen for all the tests used in the statistical evaluation of the results.

### Results

In table 1 are reported all the cases of primary malignant melanoma of the skin. In this series cases with metastases at the moment of the diagnosis were ruled out.

In table 2 are reported the 1,458 cases distributed according to the age and sex.

In table 3 the distribution according to the site of melanoma is reported.

From this table 27 cases (8 males and 19 females) were excluded due to the lack of the precise site of primary melanoma. In order to verify whether or not there was a relationship

TABLE 1: number of primary melanomas of the skin recorded in the period 1975-2000.

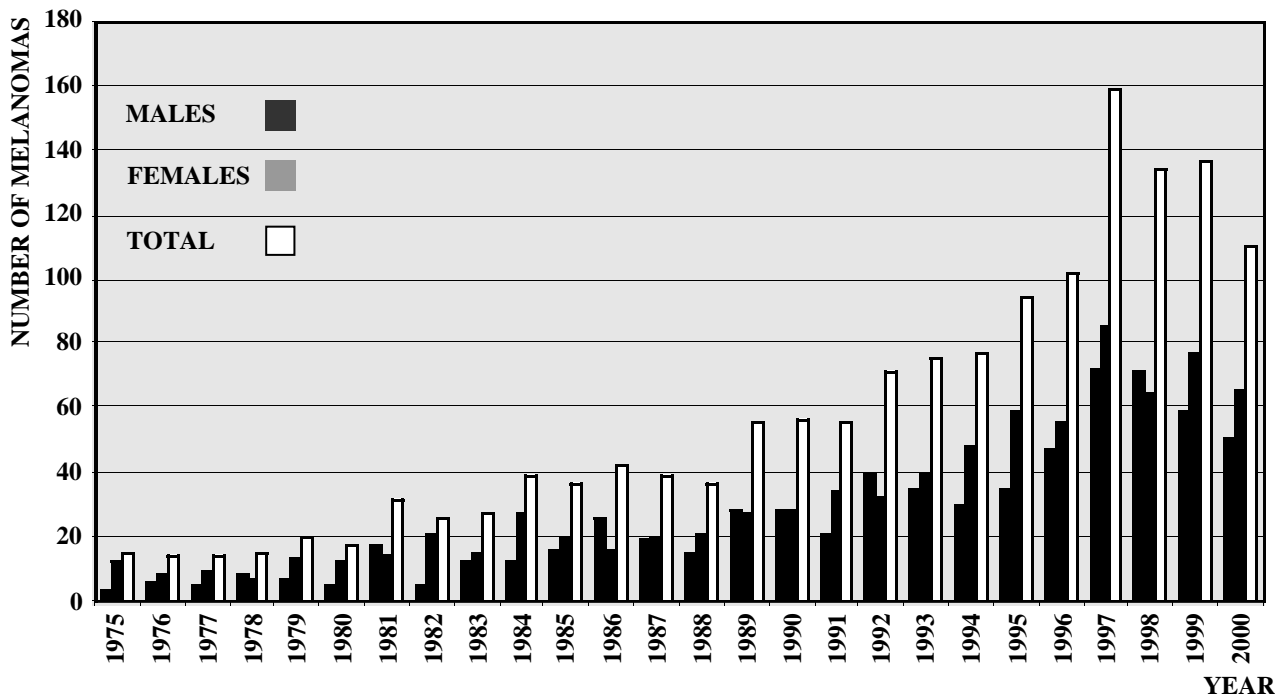


TABLE 2: age and sex in 1,458 cases of melanoma.

AGE*	MALES	FEMALES	CASES
3	1	0	1
6	1	0	1
8	1	0	1
13	1	2	3
16	0	2	2
17	0	1	1
18	0	3	3
19	2	3	5
20	1	5	6
21	5	7	12
22	2	3	5
23	5	2	7
24	5	2	7
25	3	6	9
27	4	12	16
28	2	10	12
29	5	9	14
30	14	10	24
31	10	10	20
32	1	16	17
33	10	15	25
34	6	8	14
35	5	13	18
36	12	18	30
37	4	12	16
38	6	11	17
39	12	23	35
40	16	15	31
41	11	21	32
42	9	22	31
43	7	16	23
44	14	18	32
45	6	16	22
46	8	8	16
47	11	14	25
48	21	15	36
49	18	24	42
50	20	14	34
51	8	15	23
52	9	19	28
53	11	13	24
54	12	8	20
55	17	13	30
56	21	17	38
57	8	20	28
58	14	10	24
59	18	14	32
60	22	21	43
61	6	11	17
62	18	14	32
63	17	11	28
64	12	15	27
65	12	17	29
66	15	16	31
67	10	10	20
68	17	18	35
69	11	9	20
70	13	15	28
71	16	17	33
72	15	11	26
73	7	9	16
74	13	7	20
75	14	11	25
76	6	16	22
77	11	5	16
78	45	7	12
79	5	5	10
80	4	5	9
81	6	3	9
82	5	7	12
83	4	4	8
84	2	4	6
85	2	3	5
86	0	1	1
87	0	3	3
88	0	1	1
89	1	2	3
90	0	3	3
91	0	1	1
97	0	1	1
98	0	1	1
<b>TOTAL</b>	<b>648</b>	<b>810</b>	<b>1458</b>

\*Age (yrs)

between sex and site of melanoma, a  $\chi$ -square independence test was carried out, aggregating the data regarding head and neck and the data regarding trunk and genitalia. According to the results of the test  $-\chi$ -square = 96,6636, k = 3 d.o.f. (degrees of freedom), p value = 0-, the null hypothesis ( $H_0$ ) of lack of association between sex and site of melanoma was rejected. Therefore, the two variables are significantly associated.

When considering the figures and percentages, the trunk is more frequently affected in

TABLE 3: age and sex in 1,431 cases of melanoma.

SITE	MALES	FEMALES	TOTAL
HEAD	110	128	238
NECK	3	7	10
TRUNK	327	220	547
GENITALIA	2	11	13
UPPER LIMB	71	98	169
LOWER LIMB	127	327	454
<b>TOTAL</b>	<b>640</b>	<b>791</b>	<b>1431</b>

males, whereas the lower limb is more frequently involved in females.

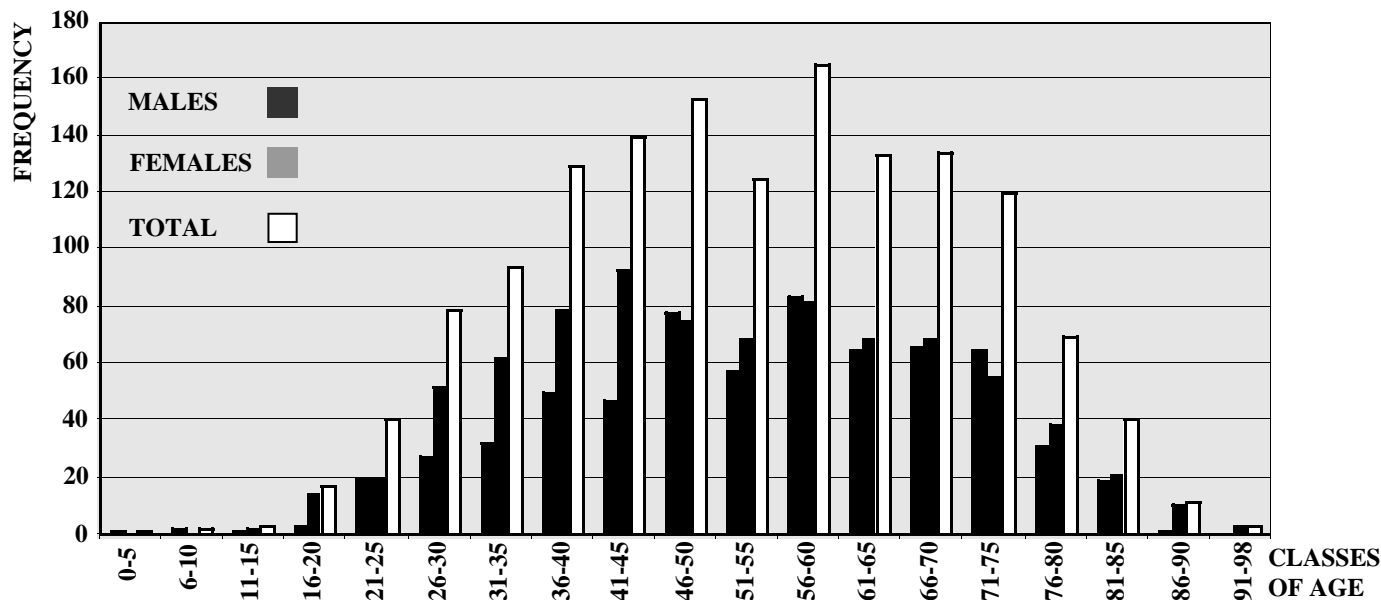
**Comment**

From 1975 (15 cases) to 1980 (17 cases) the cases of melanoma did not increase. However in 1981 the number of cases was 31, 10 years later in 1981 the number of cases almost doubled (56), and doubled again in 2000 (111), confirming even in Bari the trend reported by other Authors (3) of a 10% increase per year of this malignant tumor.

With regard to the sex (table 2) even in Bari the number of affected females (55%) slightly overcomes that one of males.

With regard to the age, the most affected age is between 36 and 75 years, as evident in table 2 and even in table 4, which groups the cases in 5-year classes. More than 75% of cases are included between 36 and 75 years, 8.4% of cases are included between 75 and 98 years, 11.9% of cases are included between 26 and 35 years, 3.9% of cases are included between 16 and 25 years and 0.4% of cases are present under 16 years. Prepubertal melanoma -0 to 12 years- accounts for 0.2% of cases.

**TABLE 4: cases of melanoma distributed in 5-year classes.**



**Site distribution of melanoma**

Most authorities agree that melanoma more frequently affects the trunk in males and the lower limb in females (4). However, the factors responsible for the different distribution in the two sexes are not yet elucidated. Hormonal factors probably influence the different distribution, although the mechanisms of their activity are not clear. To answer this question, first of all we recorded the percentage distribution according to the site involved of the total population (table 5), aimed at comparing the data of the female and male groups, which were different in size.

**TABLE 5: 1,431 cases of melanoma distributed according to the site and sex.**

SITE	MALES	FEMALES	TOTAL
HEAD	17.19%	16.18%	16.63%
NECK	0.47%	0.88%	0.70%
TRUNK	51.09%	27.81%	38.22%
GENITALIA	0.31%	1.39%	0.91%
UPPER LIMB	11.09%	12.39%	11.81%
LOWER LIMB	19.84%	41.34%	31.73%

TABLE 5: histograms of distribution of 1,431 cases of melanoma according to the site and sex.

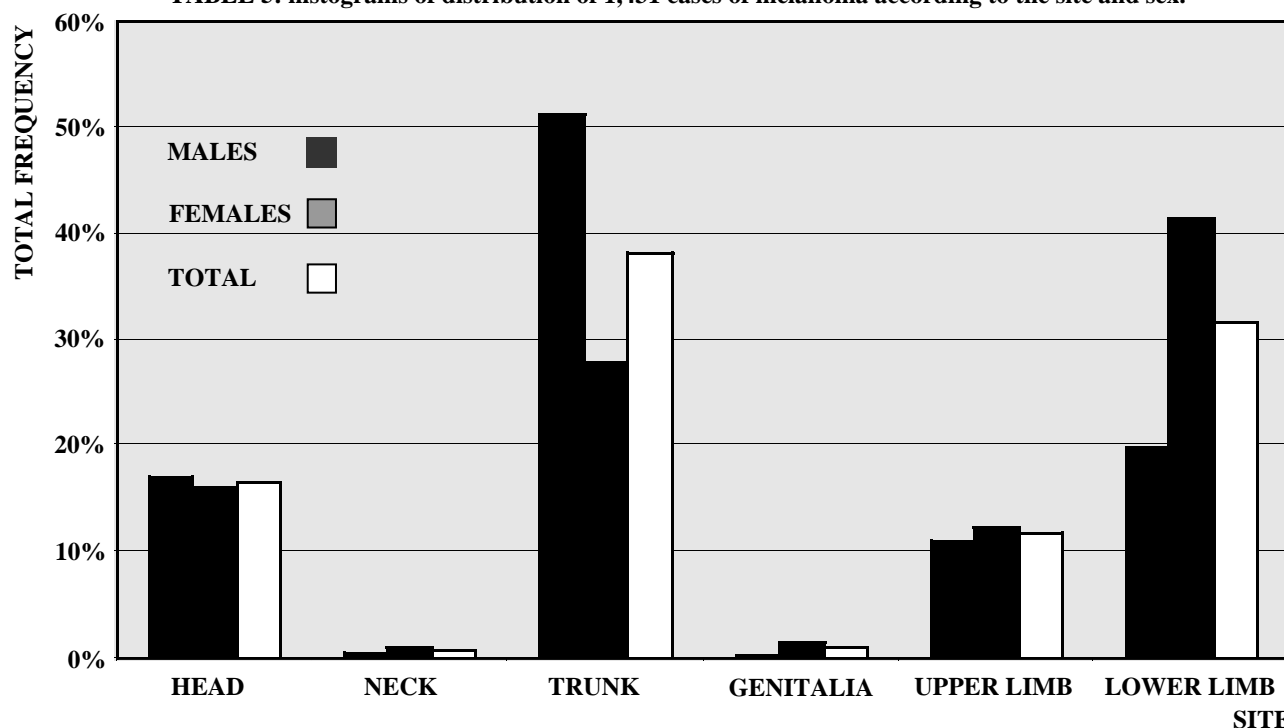


Table 5 shows an increased localization of melanoma on the trunk, followed by the lower limb, the head and the upper limb. We should take into account, however, the different surface of these body areas according to the rule of nine. According to the latter, we should double the frequency of the head and cut by half that one of the lower limb and trunk. Doing this way the real concentration per square centimeter of melanoma is more frequent on the head, followed by the trunk, the lower limb and finally the upper limb. Physicians should take into account this consideration when talking about an increased concentration of melanoma in sites as the trunk, which are intermittently exposed to sun radiations.

Corrected figures are not necessary when studying the different site distribution according to the sex. In table 5 you can see that there is not difference between the two sexes with regard to the distribution on the head and upper limbs. As a matter of fact, the comprehensive percentage of localization on the head is 16.63% -17.19 in males and 16.18 in females- and on the upper limb is 11.81% -11.09% in males and 12.39% in females-.

With regard to the localization on the head, the null hypothesis ( $H_0$ ) that the percentage localization on the head does not depend on the sex is accepted. As a matter of fact, in the 2-sample test for equality of proportions,  $\chi$ -square = 0.1905, d.o.f. = 1, p value = 0.6625.

Even for the localization on the upper limb the null hypothesis ( $H_0$ ) that the involvement of the upper limb does not depend on the sex is accepted. As a matter of fact, in the 2-sample test for equality of proportions  $\chi$ -square = 0.4526, d.o.f. = 1, p value = 0.5011.

There is apparently a different behavior in the two sexes with regard to the genitalia with a comprehensive percentage of 0.91% -0.31% in males and 1.39% in females- and at a minor extent with regard to the neck with a comprehensive percentage of 0.70% -0.47% in males and 0.88% in females-. However, the number -23- of cases of melanoma in these sites is too small to draw statistically significant conclusions. Due to this reason in the statistical evaluation the data of the neck were aggregated to the head and those ones of the genitalia to the trunk.

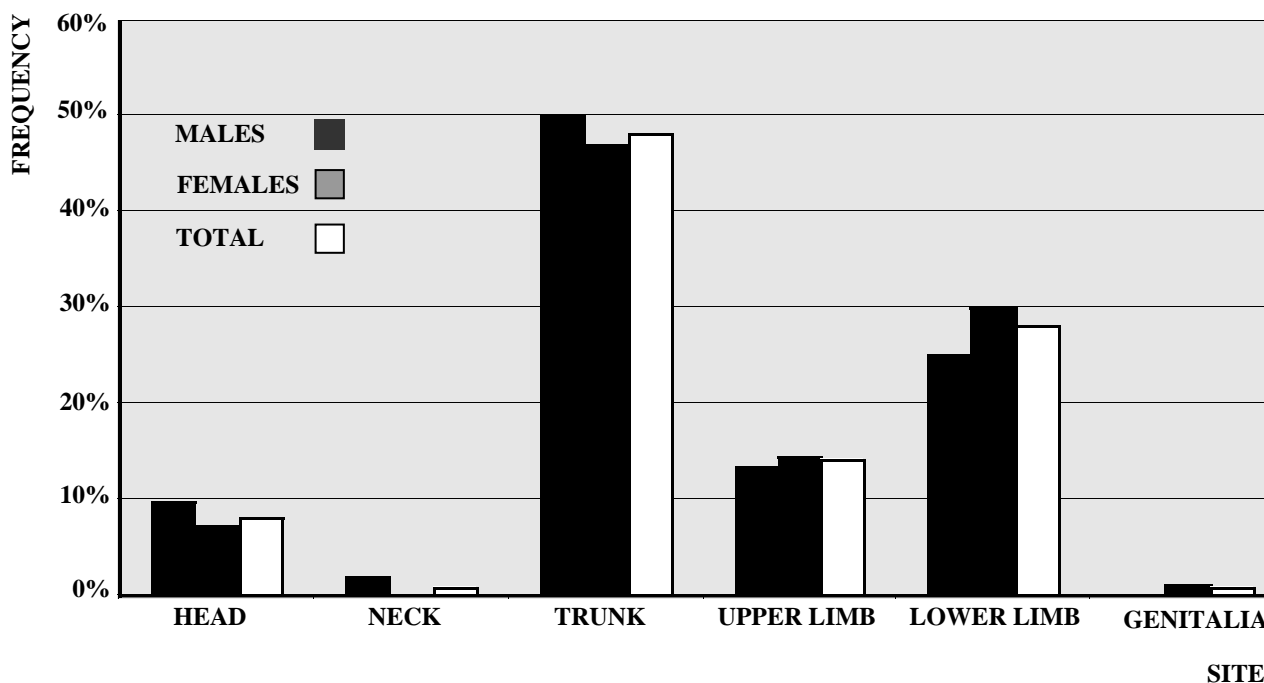
The different distribution of the cases of melanoma on the trunk -51.09% in males and

27.81 in females- and on the lower limb - 19.84% in males and 41.34% in females- affects the result of the statistical analysis when comprehensively considering all the sites and asking whether or not there is association between sex and site localization. As a matter of fact, as above mentioned the null hypothesis of independence is rejected.

In order to clarify the causal factors, which are responsible for the different distribution in the two sexes, we divided the whole population in classes of age. In the first class or prepubertal class, from 0 to 15 years, we have only 5 cases.

Therefore, a statistical evaluation of these data is impossible. Another report (1) of this issue, which investigates the site distribution of 289 cases of melanoma in subjects under 13 years collected in the relevant world literature, clearly shows that the site distribution of melanoma in this period of the life is significantly different. The subsequent classes of age were 16-30 years (table 6), 31-40 years (table 7), 41-50 (table 8), 51-60 (table 9) and finally more than 60 (table 10). The number and percentage distribution with histograms according to the site and sex was reported in all these classes of age.

**TABLE 6: 130 cases of melanoma distributed according to the site and sex (16-30 years).**



SITE	MALES	FEMALES	TOTAL
HEAD	4	6	10
NECK	1	0	1
TRUNK	26	39	65
UPPER LIMB	7	11	18
LOWER LIMB	12	23	35
GENITALIA	0	1	1
TOTAL	50	80	130

SITE	MALES	FEMALES	TOTAL
HEAD	8.00%	7.50%	7.69%
NECK	2.00%	0%	1.54%
TRUNK	52.00%	48.75%	50.00%
UPPER LIMB	14.00%	13.75%	13.85%
LOWER LIMB	24%	28.75%	26.92%
GENITALIA	0%	1.37%	0.77%

In the 16-30 years class, namely young post-pubertal class (table 6) there are 130 cases, with 50 males -38.46%- and 80 females -61.54%-, thus a more significant difference with regard to the sex as compared with the whole population. Surprisingly enough, in this class of age malignant melanoma is characterized by similar localization in the two sexes. Particularly, the trunk is affected in 52% of males and 48.75% of females, whereas the lower limb is involved in 24% of males and 28.75% of females.

Using the  $\chi$ -square test of Pearson, the null hypothesis that the distribution on the different sites does not depend on the sex is accepted - $\chi$ -square = 0.4526, d.o.f. = 1, p value = 0.501-, although there are some doubts in the distribution of the test. Particularly, using the 2-sample test for equality of proportions, the localization on the trunk in the 16-30 years class of age does not depend on the sex, because the null hypothesis of equality is accepted  $\chi$ -square = 0.0325, d.o.f. = 1, p value = 0.8569. Also the localization on lower limb in the 16-30 years class does not depend on the sex, because the null hypothesis of equality is accepted - $\chi$ -square = 0.1527, d.o.f. = 1, p value = 0.6959-.

In this class of age, even applying the rule of nine, the trunk is more frequently affected than the head. As a matter of fact, in the 16-30 year class of age the head is minimally affected -7.69%-, whereas the percentage of involvement progressively increases in the subsequent classes -8.37% in the 31-40 year class, 9.45 in the 41-50 class, 16.19 in the 51-60 class and finally 26.17 in the over 60 class-.

Using the  $\chi$ -square test of Pearson, the null hypothesis that the distribution on the head does not depend on the age is rejected - $\chi$ -square = 61.1663, d.o.f. = 4, p value = 0-, although there are some doubts in the distribution of the test. Therefore, the localization on the head depends on the age.

The increasing involvement of the head with years is an interesting finding of our study. This finding can be hardly explained when compared with the percentage of involvement of the head in the prepubertal melanoma (1), why is relatively high -27.76%- and in apparent contrast with the trend of adults.

As a matter of fact, the null hypothesis that the percentage involvement of the head in the child -78/281, 27.76%- is equal to that one of adults -238/1,431, 16.63%- is rejected in the 2-sample test for equality of proportions - $\chi$ -square = 18.5865, d.o.f. = 1, p value = 0-.

With regard to the adult, the hypothesis that the chronic sun exposure is responsible for the involvement of the head is in agreement with the behavior of the skin cancer, but in contrast with the hypothesis of intermittent, recreational sun exposure, usually used to explain the localization on the trunk, especially in the male.

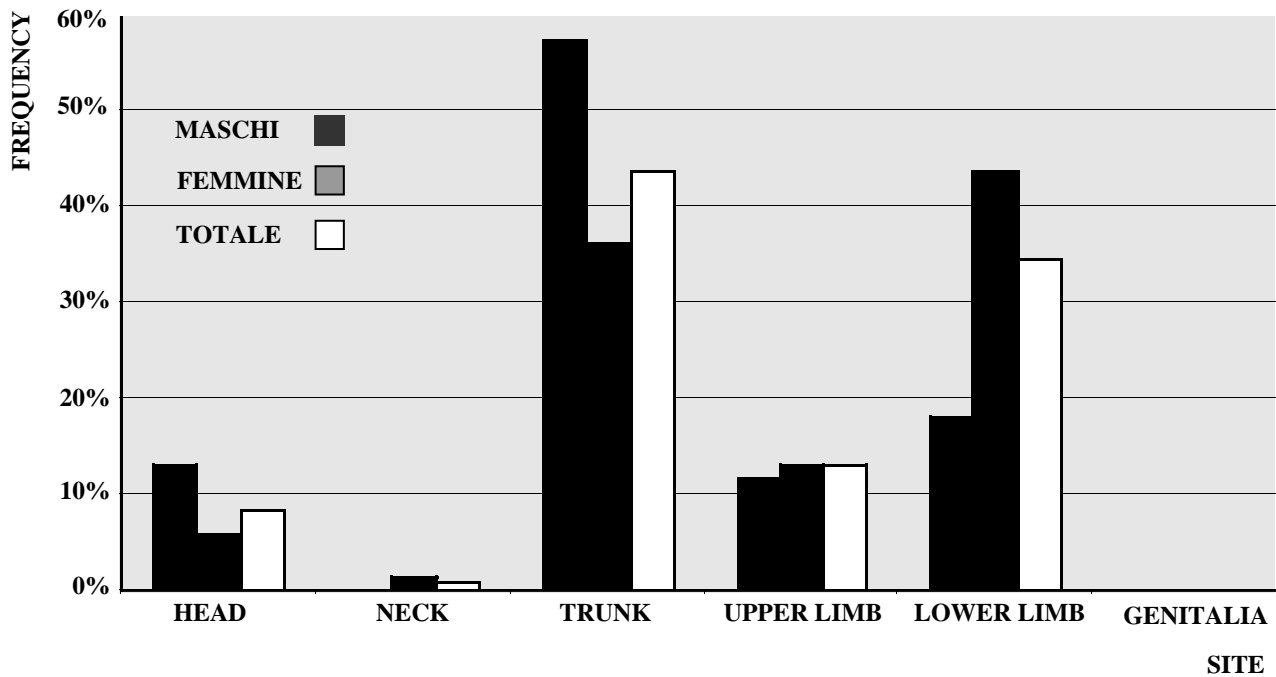
On the other hand, physicians should remember that the surface of the head is 4 times smaller than the trunk. Taking into account this correction, the prevalence of melanoma for surface unit is larger on the head than on the trunk.

The increased prevalence of head localization with years in adults is apparently in contrast with the high percentage of melanoma of the head in the prepubertal age (1). However, the contrast is only apparent, because the localization on the head in the child depends on the involvement of the scalp, which is not a sun exposed area, in about half cases -36/75-, whereas in the adult the face is mainly affected. As a matter of fact, among 238 cases localized on the head, 16 affect the scalp, whereas 208 cases affect the face.

Probably, other factors are involved in the localization on the scalp in the child, as supported by the presence on the scalp in about half cases of a congenital, often giant nevus, especially in melanoma affecting the first years of life.

The significant involvement of the head in prepubertal melanoma is confirmed by other Authors (5) in 31 patients aged 0-21 years, whereas contrasting data are reported by other Authors (2, 6, 7). According to Spatz et Al. (6) in a European series of malignant melanoma in 60 subjects aged 0-16 years, the head is affected in 18% of cases without sexual differences. Other Authors (2, 7) show a different involvement of the head in the two sexes. Conti et Al. (2) report an involvement of 24% in males and 17% in females, Zhu et Al. respectively of 24 and 3%.

TABLE 7: 215 cases of melanoma distributed according to the site and sex (31-40 years).



SITE	MALES	FEMALES	TOTAL
HEAD	10	8	18
NECK	0	2	2
TRUNK	44	50	94
UPPER LIMB	9	18	27
LOWER LIMB	14	60	74
GENITALIA	0	0	0
TOTAL	77	138	215

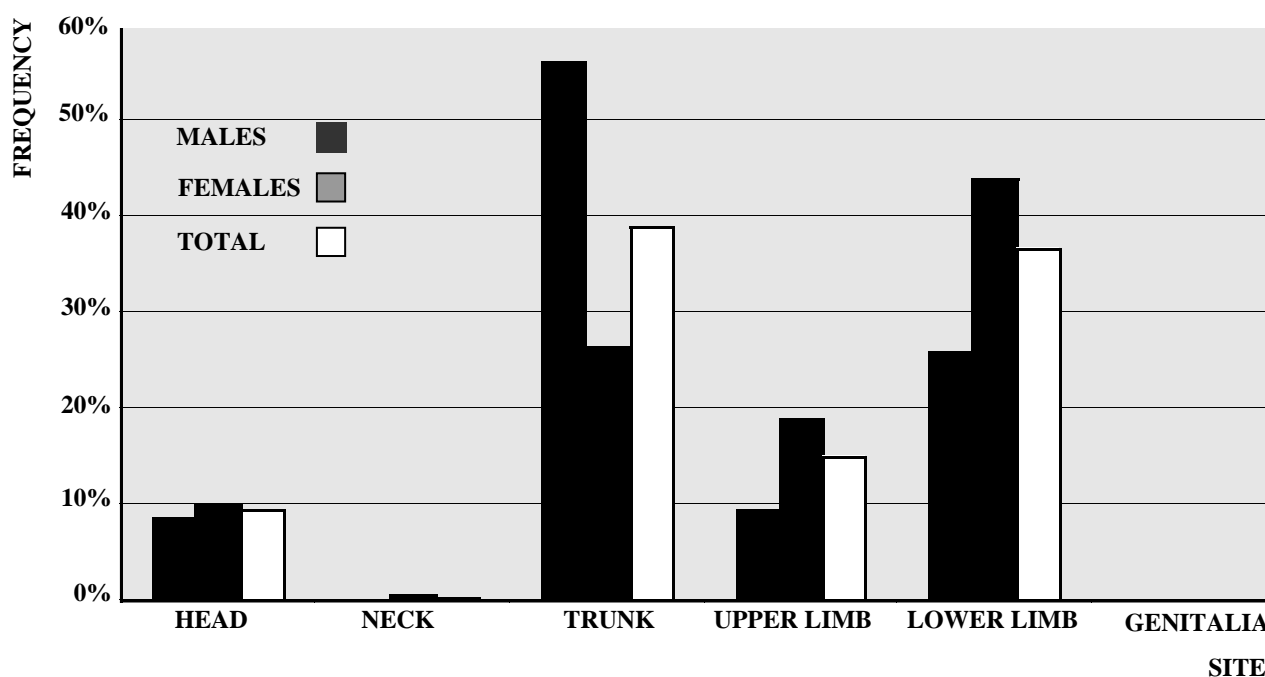
SITE	MALES	FEMALES	TOTAL
HEAD	12.99%	5.80%	8.37%
NECK	0%	1.45%	0.93%
TRUNK	57.14%	36.23%	43.72%
UPPER LIMB	11.69%	13.04%	13.02%
LOWER LIMB	18.18%	43.48%	34.41%
GENITALIA	0%	0%	0%

In the 31-40 year class of age (table 7), using the  $\chi$ -square test of Pearson, the null hypothesis that the distribution of melanoma in the different sites does not depend on the sex is rejected  $-\chi$ -square = 15.9549, d.o.f. = 3, p value = 0.0012-. Particularly, using the 2-sample test for equality of proportions, the localization on the trunk in the 31-40 year class of age depends on the sex,

because the null hypothesis of equality is rejected  $-\chi$ -square = 7.9537, d.o.f. = 1, p value = 0.0048-.

Like the trunk, even the localization on the lower limb in the 31-40 year class of age depends on the sex, because the null hypothesis of equality is rejected  $-\chi$ -square = 12.913, d.o.f. = 1, p value = 0.00038-.

TABLE 8: 275 cases of melanoma distributed according to the site and sex (41-50 years).



SITE	MALES	FEMALES	TOTAL
HEAD	10	16	26
NECK	0	1	1
TRUNK	65	42	107
UPPER LIMB	11	30	41
LOWER LIMB	30	70	100
GENITALIA	0	0	0
<b>TOTAL</b>	<b>116</b>	<b>159</b>	<b>275</b>

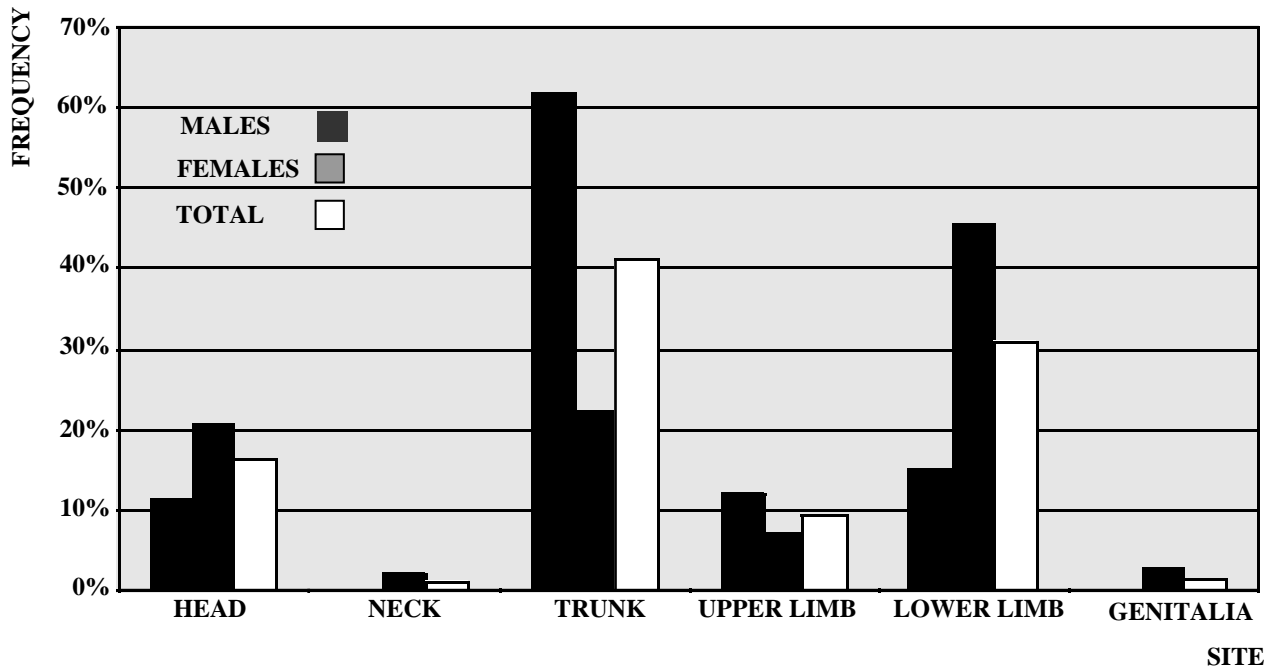
SITE	MALES	FEMALES	TOTAL
HEAD	8.62%	10.06%	9.45%
NECK	0%	0.63%	0.36%
TRUNK	56.03%	26.41%	38.91%
UPPER LIMB	9.48%	18.87%	14.91%
LOWER LIMB	25.86%	44.02%	36.73%
GENITALIA	0%	0%	0%

In the 41-50 year class of age (table 8), using the  $\chi$ -square test of Pearson, the null hypothesis that the distribution of melanoma in the different sites does not depend on the sex is rejected  $-\chi$ -square = 25.4625, d.o.f. = 3, p value = 0-. Particularly, using the 2-sample test for equality of proportions, the localization on the trunk in the 41-50 year class of age clearly depends on

the sex, because the null hypothesis of equality is rejected  $-\chi$ -square = 23.5237, d.o.f. = 1, p value = 0-.

Like the trunk, even the localization on the lower limb in the 41-50 year class of age depends on the sex, because the null hypothesis of equality is rejected  $-\chi$ -square = 8.7928, d.o.f. = 1, p value = 0.003-.

TABLE 9: 278 cases of melanoma distributed according to the site and sex (51-60 years).



SITE	MALES	FEMALES	TOTAL
HEAD	15	30	45
NECK	0	3	3
TRUNK	82	32	114
UPPER LIMB	16	10	26
LOWER LIMB	20	66	86
GENITALIA	0	4	4
TOTAL	133	145	278

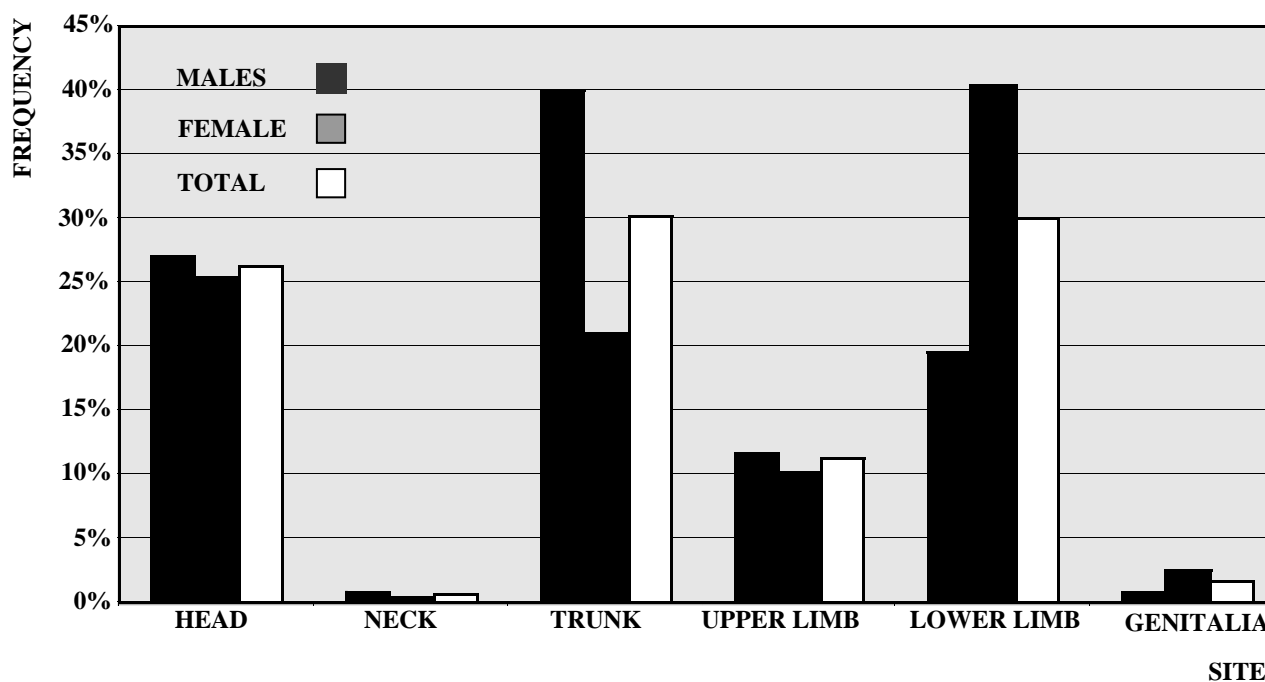
SITE	MALES	FEMALES	TOTAL
HEAD	11.28%	20.69%	16.19%
NECK	0%	2.07%	1.08%
TRUNK	61.65%	22.07%	41.01%
UPPER LIMB	12.03%	6.90%	9.35%
LOWER LIMB	15.04%	45.52%	30.93%
GENITALIA	0%	2.76%	1.44%

In the 51-60 year class of age (table 9), using the  $\chi$ -square test of Pearson, the null hypothesis that the distribution of melanoma in the different sites does not depend on the sex is rejected  $-\chi$ -square = 50.2471, d.o.f. = 3, p value = 0-. Particularly, using the 2-sample test for equality of proportions, the localization on the trunk in the 51-60 year class of age depends on the sex,

because the null hypothesis of equality is rejected  $-\chi$ -square = 7.9537, d.o.f. = 1, p value = 0.0048-.

Like the trunk, even the localization on the lower limb in the 51-60 age-class depends on the sex, because the null hypothesis of equality is rejected  $-\chi$ -square = 43.3131, d.o.f. = 1, p value = 0-.

TABLE 10: 489 cases of melanoma distributed according to the site and sex (> 60 years).



SITE	MALES	FEMALES	TOTAL
HEAD	65	63	128
NECK	2	1	3
TRUNK	96	52	148
UPPER LIMB	28	25	55
LOWER LIMB	47	100	147
GENITALIA	2	6	8
TOTAL	240	247	489

SITE	MALES	FEMALES	TOTAL
HEAD	27.08%	25.51%	26.17%
NECK	0.83%	0.40%	0.61%
TRUNK	40%	21.05%	30.26%
UPPER LIMB	11.67%	10.12%	11.25%
LOWER LIMB	19.58%	40.48%	30.06%
GENITALIA	0.83%	2.43%	1.63%

In the over 60 year class of age (table 10), using the  $\chi$ -square test of Pearson, the null hypothesis that the distribution of melanoma in the different sites does not depend on the sex is rejected  $-\chi$ -square = 29.5092, d.o.f. = 3, p value = 0-. Particularly, using the 2-sample test for equality of proportions, the localization on the trunk in the over 60 year class of age depends on

the sex, because the null hypothesis of equality is rejected  $-\chi$ -square = 719.7713, d.o.f. = 1, p value = 0-.

Like the trunk, even the localization on the lower limb in the over 60 year class of age depends on the sex, because the null hypothesis of equality is rejected  $-\chi$ -square = 24.2548, d.o.f. = 1, p value = 0-.

After 30 years, the distribution according to the site in the two sexes is apparently uniform. We already mentioned the progressively increasing involvement of the head with age. On the other hand, the involvement of the trunk is inversely related to increasing age, changing from 50% in the 16-30 year class, to 43.72% in the 31-40 year class and then to 38.91%, 41.01% and 30.26% in the subsequent classes, respectively 41-50, 51-60 and over 60. Using the 5-sample test for equality of proportions, the null hypothesis that the localization on the trunk is equal in the different class of age is rejected -  $\chi$ -square = 5.5146, d.o.f. = 4, p value = 0.0001-.

The localization on the lower limb is less consistent with increasing age. Namely there is an increased involvement of the lower limb when passing from the 16-30 to the 31-40 year class of age -from 26.92% to 34.41%- and to 41-50 - 36.73%. On the other hand, there is a decreased involvement of the lower limb in the subsequent age class -30.93% in the 51-60 year class of age and 30.06% in the over 60 class of age-. Using the 5-sample test for equality of proportions, the null hypothesis that the localization on the lower limb is equal in the different classes of age is accepted - $\chi$ -square = 24.4917, d.o.f. = 4, p value = 0.2384-. Therefore, the localization on the lower limb does not depend on the age in the total population.

The localization on the upper limb is stable with age -13.85% in the youngest class of age, 13.02%, 14.91%, 9.35 and finally 11.25% in the over 60 year class of age. Using the 5-sample test for equality of proportions, the null hypothesis that the localization on the upper limb is equal in the different classes of age is accepted -  $\chi$ -square = 4.7783, d.o.f. = 4, p value = 0.3118-. Therefore, the localization on the upper limb does not depend on the age.

In table 11 is shown the ratio between the localization on the trunk and lower limb in the two sexes with years. In the male the ratio is not related to the age and always higher than 1, ranging from 2.04 to 4.1, whereas in the female the ratio is higher than 1 only in the 16-30 class and then decreases with age, from 1.69 in the youngest class to 0.83, 0.60, 0.48 and 0.52 in the subsequent classes of age.

**TABLE 11: Ratio between localization on the trunk and lower limb in the two sexes according to the classes of age.**

CLASSES OF AGE	MALES	FEMALES
16-30	2.17	1.69
31-40	3.14	0.83
41-50	2.16	0.60
51-60	4.10	0.48
>60	2.04	0.52

In conclusion, the predilection for the trunk in males and the lower limb in females gets evident only after 30 years and persists after 60. This finding does not support a significant role of sex-linked hormonal factors. Moreover, the localization on the head progressively increases with years. This finding is similar to that one of skin cancer.

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