SUPPLEMENT

Initial QC

Initial QC had already been carried out on each of the GWAS studies (Supplemental Table VI), using the GENEVA protocol or protocols that were similar. Some of the pertinent QC parameters used for each of the studies are included in Supplemental Table VII.

Imputation

The imputation was done by first matching the strand of the GWAS data with the 1KGP data after excluding ambiguous A/T or C/G SNPs. We used the 1kGP reference panel (1092 samples; v2.20101123 for GECCO; v3.20101123 for GARNET, HIPFX, MOPMAP, and WHIMS+). The GWAS data were split into chunks with each chunk having 10,000 SNPs and neighboring chunks have 1000 overlapping SNPs. Then all chunks were phased using Beagle and then combined using mergebeaglechunks.jar (available from the BEAGLE website). An autoclip file was created for minimac to specify what the range of the chunks (start and stop) and the SNPs to be imputed within the chunk (core_start and core_end) so that no SNP needed to be be imputed twice. All chunks were imputed into 1kGP using minimac. SNPs that could not be imputed with high enough confidence (cut-off $R^2 > 0.1$) were omitted for that particular study (but still appear as columns of missing data in files if they were kept in the other studies, to facilitate alignment). We did not impute the X chromosome. The SHARe study was independently imputed to the same reference panel. The procedures used were similar to those listed above, except that MACH was used to carry out the imputation.

Harmonization

A panel of 5665 SNPs was used for checking the pairwise concordance among all samples in GARNET, GECCO, HIPFX, SHARe, WHIMS+, and MOPMAP. The same panel of SNPs was used for principal component check together with HapMap samples to identify ethnicity outlier. The same panel of SNPs were used for checking IBD in plink to identify relatedness among samples. Another principal component analysis was done for combined samples (after removing of ineligible duplicates) in all studies then the resulting PCs were mapped back to samples within each study. A NetCDF file of imputed results was created for each chromosome in each study. Different studies have the same set of SNPs — SNPs that were not successfully imputed in a particular study but are in other studies are listed as missing values. A SNP info file was also created along with each NetCDF file describing the SNP name, chromosome, position, count allele, alternative allele, count allele frequency, and imputation quality for each SNP.

Duplicates

Because subjects for each of these GWAS were selected independently, we checked for duplicates between the studies. We removed a small number of samples that were supposed to be duplicates but had a concordance rate <90% and appeared to be duplicates but were from unrelated individuals who appeared not to be monozygotic twins. We kept samples that were monozygotic twins (see relatedness below), and duplicates between studies in our datasets. There currently are 29,846 unique subjects in the data.

Relatedness

We carried out an IBD analysis using a subset of 5665 SNPS and the PLINK package. We used the results to identify 42 parent off-spring pairs and 303 pairs of siblings/first-degree relatives. We did not identify second and higher degree relatives (eg, cousins, half-siblings, etc).

Genetic risk score (GRS) calculation

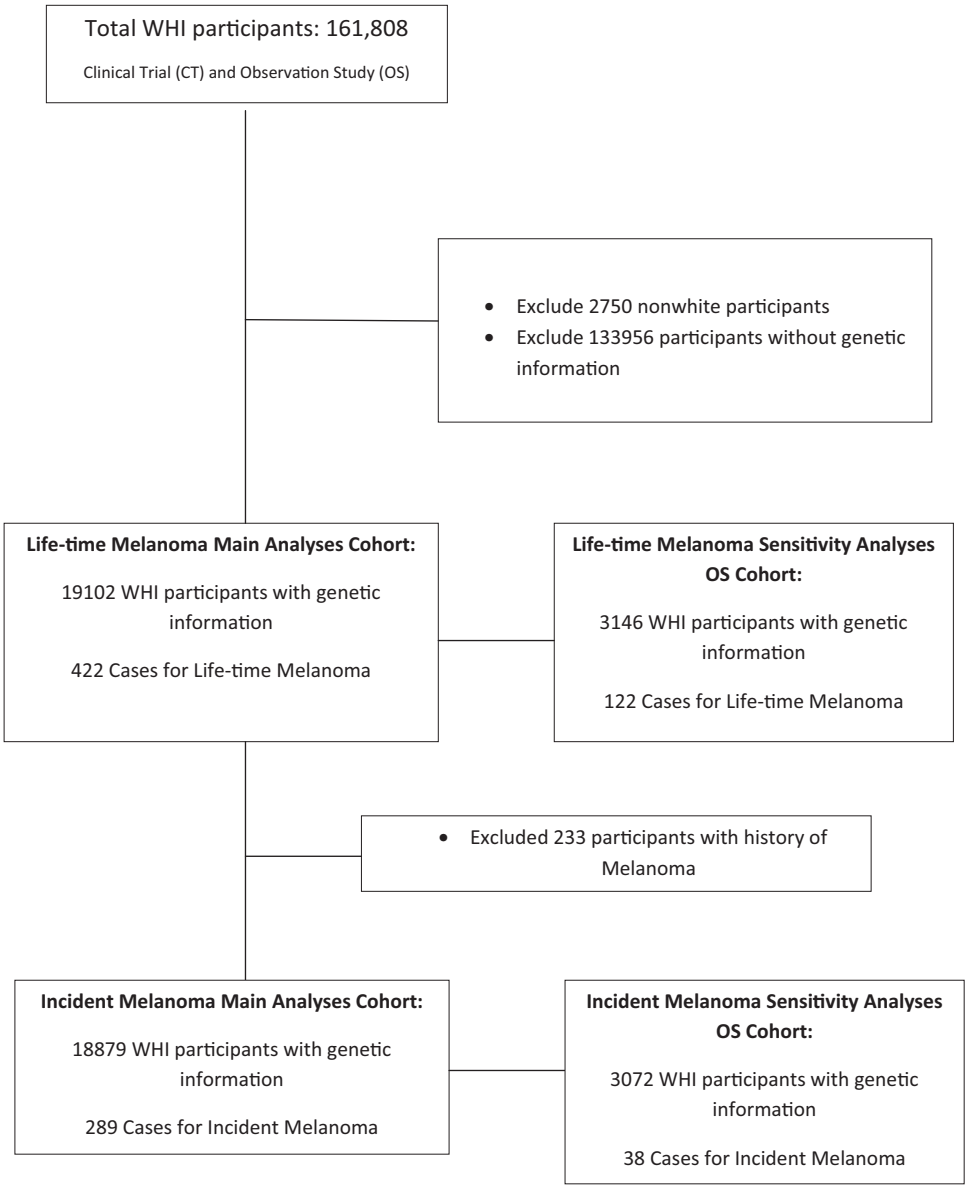
Beta coefficients of 21 SNPs reported in published literature were used as weights and the following formula was applied to calculate the genetic risk score:

$$\mathrm{GS} = \sum_{s=1}^{21} W_s \sum_{k=1}^{2} EA_{sk}$$

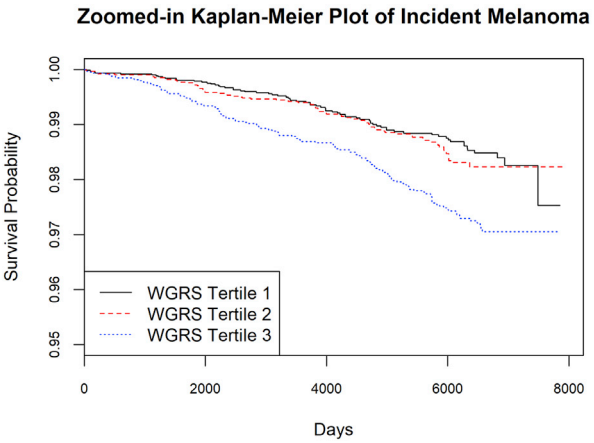
where EA is an indicator for the presence of effect alleles at allele k at SNP s (s = 0,1) and W_s represents the beta coefficient estimates of effect allele of SNP s from published literature. We verified that the effect allele and allele frequency we used in our study matched with the alleles and allele frequency listed in the published literature.

Area under curve (AUC) calculation

To assess the performance of the predictive capability of the GRS for incident melanoma, the c-index was calculated using rcorr.cens function in the Hmisc package.[9] The c-index was calculated based on a model including the covariates described earlier with and without the GRS tertiles.[10] We calculated the AUC for lifetime melanoma models using pROC package.[11] To calculate the confidence interval of the difference, we bootstrapped the sample 1000 times in each imputation and calculated the difference for c-index/AUC for each bootstrapped sample. The observed mean and standard deviation of the difference of c-index/AUC for each imputation were pooled using Rubin's rules[12] to obtain a 95% confidence interval.



Supplemental Fig 1. Diagram of analytic population. A total of 19,102 white women with genotype information were included in the study. This included 422 lifetime melanoma cases and 289 incident melanoma cases.



Supplemental Fig 2. Kaplan–Meier plot for incident melanoma in Women's Health Initiative cohort. Compared to the lowest tertile of genetic risk score, the highest tertile of genetic risk score was associated with higher incident melanoma during >20 years of follow-up, with a hazard ratio of 1.89 for the highest tertile as compared to the lowest tertile (95% confidence interval 1.42-2.52).

Supplemental Table I. Demographics of the whole cohort

	Women with weighted GRS (N = 19,102)	Women with weighted GRS but no history of melanoma (n = 18,879)	GRS first tertile (n = 6252)	GRS second tertile (n = 6254)	GRS third tertile (n = 6506)
Region, n (%)					
Northeast	5064 (26.6)	5034 (26.7)	1702 (27.2)	1660 (26.5)	1702 (26.2)
South	3888 (20.5)	3854 (20.4)	1253 (20)	1290 (20.6)	1345 (20.7)
Midwest	4724 (24.8)	4703 (24.9)	1482 (23.7)	1555 (24.9)	1687 (25.9)
West	5336 (28.1)	5288 (28)	1815 (29)	1749 (28)	1772 (27.2)
Education, n (%)					
High school	4839 (25.5)	4814 (25.5)	1622 (25.9)	1562 (25)	1655 (25.4)
College	9476 (49.8)	9411 (49.8)	3062 (49)	3162 (50.6)	3252 (50)
Beyond college	4625 (24.3)	4583 (24.3)	1542 (24.7)	1503 (24)	1580 (24.3)
Missing	72 (0.4)	71 (0.4)	26 (0.4)	27 (0.4)	19 (0.3)
Latitude, n (%)					
Southern, <35°N	4618 (24.3)	4577 (24.2)	1554 (24.9)	1534 (24.5)	1530 (23.5)
Middle, 35-40°N	5333 (28.1)	5285 (28)	1769 (28.3)	1718 (27.5)	1846 (28.4)
Northern, >40°N	9061 (47.7)	9017 (47.8)	2929 (46.8)	3002 (48)	3130 (48.1)
Langley (g-cal/cm^2), n (%)					
300-325	6349 (33.4)	6321 (33.5)	2050 (32.8)	2104 (33.6)	2195 (33.7)
350	4425 (23.3)	4393 (23.3)	1443 (23.1)	1446 (23.1)	1536 (23.6)
375-380	1912 (10.1)	1895 (10)	607 (9.7)	630 (10.1)	675 (10.4)
400-430	2881 (15.2)	2859 (15.1)	961 (15.4)	950 (15.2)	970 (14.9)
475-500	3445 (18.1)	3411 (18.1)	1191 (19)	1124 (18)	1130 (17.4)
Smoke, n (%)					
Never smoked	9509 (50)	9450 (50.1)	3122 (49.9)	3102 (49.6)	3285 (50.5)
Past smoker	7770 (40.9)	7702 (40.8)	2596 (41.5)	2549 (40.8)	2625 (40.3)
Current smoker	1514 (8)	1509 (8)	457 (7.3)	527 (8.4)	530 (8.1)
Missing	219 (1.2)	218 (1.2)	77 (1.2)	76 (1.2)	66 (1)
Take multivitamin, n (%)					
No	18,204 (95.8)	18,076 (95.7)	5977 (95.6)	5998 (95.9)	6229 (95.7)
Yes	808 (4.2)	803 (4.3)	275 (4.4)	256 (4.1)	277 (4.3)
Take calcium, n (%)					
No	15,056 (79.2)	14,956 (79.2)	4923 (78.7)	4940 (79)	5193 (79.8)
Yes	3956 (20.8)	3923 (20.8)	1329 (21.3)	1314 (21)	1313 (20.2)
Take vitamin D, n (%)					
No	18,258 (96)	18,132 (96)	6012 (96.2)	6004 (96)	6242 (95.9)
Yes	754 (4)	747 (4)	240 (3.8)	250 (4)	264 (4.1)
Take aspirin, n (%)					
No	14,080 (74.1)	13,977 (74)	4636 (74.2)	4642 (74.2)	4802 (73.8)
Yes	4932 (25.9)	4902 (26)	1616 (25.8)	1612 (25.8)	1704 (26.2)
Age, median (IQR)	68 (63-72)	68 (63-72)	68 (63-72)	68 (63-72)	67 (63-72)
BMI, median (IQR)	27.6 (24.2-31.7)	27.6 (24.2-31.7)	27.4 (24.1-31.5)	27.7 (24.3-31.7)	27.6 (24.1-31.7)
Total energy expended from recreational physical activity (MET hours/week), median (IQR)	7.5 (1.9-16.7)	7.5 (1.9-16.7)	7.5 (1.9-16.7)	7.5 (1.9-16.4)	7.5 (1.9-16.5)
MET hours per week from walking, median (IQR)	2 (0-6.2)	2 (0-6.2)	2 (0-6.2)	1.9 (0-6.2)	2 (0-6.2)

BMI, Body mass index; *GRS*, genetic risk score; *IQR*, interquartile range; *MET*, metabolic equivalent.

Supplemental Table II. Demographics for observational study cohort with sunscreen and skin type

	Women with weighted GRS (n = 3146)	Women with weighted GRS but no history of melanoma (n = 3072)	GRS first quartile (n = 1106)	GRS second quartile (n = 1031)	GRS third quartile (n = 1009)
Region, n (%)					
Northeast	818 (26)	803 (26.1)	282 (25.5)	254 (24.6)	282 (27.9)
South	681 (21.6)	661 (21.5)	230 (20.8)	241 (23.4)	210 (20.8)
Midwest	698 (22.2)	685 (22.3)	237 (21.4)	228 (22.1)	233 (23.1)
West	949 (30.2)	923 (30)	357 (32.3)	308 (29.9)	284 (28.1)
Education, n (%)					
High school	633 (20.1)	619 (20.1)	227 (20.5)	199 (19.3)	207 (20.5)
College	1563 (49.7)	1527 (49.7)	514 (46.5)	532 (51.6)	517 (51.2)
Beyond college	935 (29.7)	911 (29.7)	358 (32.4)	295 (28.6)	282 (27.9)
Missing	15 (0.5)	15 (0.5)	7 (0.6)	5 (0.5)	3 (0.3)
Latitude, n (%)					
Southern, <35°N	857 (27.2)	832 (27.1)	311 (28.1)	297 (28.8)	249 (24.7)
Middle, 35-40°N	904 (28.7)	879 (28.6)	323 (29.2)	294 (28.5)	287 (28.4)
Northern, >40°N	1385 (44)	1361 (44.3)	472 (42.7)	440 (42.7)	473 (46.9)
Langley (g-cal/cm^2), n (%)					
300-325	1006 (32)	992 (32.3)	347 (31.4)	313 (30.4)	346 (34.3)
350	651 (20.7)	635 (20.7)	222 (20.1)	217 (21)	212 (21)
375-380	321 (10.2)	312 (10.2)	110 (9.9)	114 (11.1)	97 (9.6)
400-430	505 (16.1)	492 (16)	177 (16)	160 (15.5)	168 (16.7)
475-500	663 (21.1)	641 (20.9)	250 (22.6)	227 (22)	186 (18.4)
Smoke, n (%)					
Never smoked	1524 (48.4)	1491 (48.5)	544 (49.2)	501 (48.6)	479 (47.5)
Past smoker	1358 (43.2)	1319 (42.9)	479 (43.3)	439 (42.6)	440 (43.6)
Current smoker	224 (7.1)	223 (7.3)	71 (6.4)	76 (7.4)	77 (7.6)
Missing	40 (1.3)	39 (1.3)	12 (1.1)	15 (1.5)	13 (1.3)
Take multivitamin, n (%)					
No	2993 (95.1)	2922 (95.1)	1060 (95.8)	981 (95.2)	952 (94.4)
Yes	153 (4.9)	150 (4.9)	46 (4.2)	50 (4.8)	57 (5.6)
Take calcium, n (%)					
No	2307 (73.3)	2253 (73.3)	809 (73.1)	747 (72.5)	751 (74.4)
Yes	839 (26.7)	819 (26.7)	297 (26.9)	284 (27.5)	258 (25.6)
Take vitamin D, n (%)					
No	2974 (94.5)	2905 (94.6)	1048 (94.8)	966 (93.7)	960 (95.1)
Yes	172 (5.5)	167 (5.4)	58 (5.2)	65 (6.3)	49 (4.9)
Take aspirin, n (%)					
No	2285 (72.6)	2230 (72.6)	810 (73.2)	767 (74.4)	708 (70.2)
Yes	861 (27.4)	842 (27.4)	296 (26.8)	264 (25.6)	301 (29.8)
Skin type, n (%)					
No burn	1132 (36)	1113 (36.2)	460 (41.6)	376 (36.5)	296 (29.3)
Burn	1569 (49.9)	1524 (49.6)	482 (43.6)	513 (49.8)	574 (56.9)
Missing	445 (14.1)	435 (14.2)	164 (14.8)	142 (13.8)	139 (13.8)
Used sunscreen, n (%)					
No	1378 (43.8)	1357 (44.2)	527 (47.6)	445 (43.2)	406 (40.2)
Yes	1360 (43.2)	1316 (42.8)	435 (39.3)	453 (43.9)	472 (46.8)
Missing	408 (13)	399 (13)	144 (13)	133 (12.9)	131 (13)
Age, median (IQR)	69 (64-74)	69 (64-74)	70 (64-74)	69 (64-73)	69 (64-74)
BMI, median (IQR)	25.6 (22.8-29.3)	25.6 (22.8-29.3)	25.4 (22.6-29.2)	25.8 (22.8-29.8)	25.6 (22.9-29.1)
Total energy expended from recreational physical activity (MET hours/week), median (IQR)	9.8 (3-18.8)	9.8 (3-18.5)	10 (3.5-19.2)	9 (3-17.6)	9.5 (2.5-18.6)
MET hours per week from walking, median (IQR)	3.5 (0-7.5)	3.5 (0-7.5)	3.5 (0-7.5)	3.8 (0-7.5)	2.5 (0-7.5)

BMI, Body mass index; *GRS*, genetic risk score; *IQR*, interquartile range; *MET*, metabolic equivalent.

Supplemental Table III. Association of 21 genome-wide significant melanoma single-nucleotide polymorphisms in the Women's Health Initiative cohort

SNP	Nearest gene	WHI MAF	WHI OR (95% CI)	WHI *P* value	Reported MAF	Reported OR	Reported *P* value	Reference
rs7412746	ARNT	0.49	1.01 (0.87-1.14)	.927	0.47	1.08	2.46×10^{-4}	Macgregor *et al.*, 2011
rs6750047	RMDN2 (CYP1B1)	0.46	1.01 (0.87-1.15)	.89	0.28	1.02	2.48×10^{-1}	Law *et al.*, 2015
rs13016963	CASP8	0.39	0.92 (0.78-1.06)	.234	0.38	0.94	6.93×10^{-3}	Barrett *et al.*, 2011 and Antonopoulou *et al.*, 2015
rs139996880	TERT	0.16	1.05 (0.74-1.35)	.76	0.16	1.26	2.4×10^{-11}	Law *et al.*, 2015
rs16891982*	SLC45A2	0.11	0.5 (−0.01 to 1.00)	.007	0.04	0.48	9.02×10^{-19}	Antonopoulou *et al.*, 2015
rs6914598	CDKAL1	0.32	1.02 (0.86-1.17)	.842	0.31	1.05	2.22×10^{-2}	Law *et al.*, 2015
rs1636744	AGR3	0.4	1.07 (0.94-1.21)	.31	0.41	1.04	5.59×10^{-2}	Law *et al.*, 2015
rs7023329	MTAP (CDKN2A)	0.5	0.92 (0.78-1.06)	.233	0.5	0.86	2.29×10^{-13}	Barrett *et al.*, 2011
rs10739221	TMEM38B (RAD23B, TAL2)	0.26	1.08 (0.91-1.24)	.378	0.24	1.1	7.39×10^{-5}	Law *et al.*, 2015
rs2995264	OBFC1	0.1	1.07 (0.84-1.30)	.575	0.1	1.16	2.75×10^{-5}	Law *et al.*, 2015
rs1393350*	TYR	0.25	1.21 (1.06-1.36)	.014	0.27	1.17	1.90×10^{-11}	Bishop *et al.*, 2009 and Barrett *et al.*, 2011
rs498136	CCND1	0.35	1.09 (0.95-1.23)	.242	0.36	1.09	$8.98E \times 10^{-5}$	Law *et al.*, 2015
rs1801516	ATM	0.13	1.00 (0.80-1.20)	.979	0.14	0.95	7.42×10^{-2}	Barrett *et al.*, 2011
rs4778138*	OCA2	0.18	0.70 (0.47-0.94)	.003	0.15	0.9	5.68×10^{-4}	Law *et al.*, 2015
rs258322*	MC1R	0.12	1.49 (1.29-1.70)	.0001	0.09	1.31	3.87×10^{-16}	Bishop *et al.*, 2009 and Barrett *et al.*, 2011
rs4785763*	AFG3L1P	0.33	1.31 (1.16-1.46)	.0003	0.33	1.21	3.47×10^{-18}	Bishop *et al.*, 2009 and Antonopoulou *et al.*, 2015
rs16953002	FTO	0.17	1.04 (0.86-1.23)	.633	0.17	1.01	7.54×10^{-1}	Antonopoulou *et al.*, 2015 and Iles *et al.*, 2013
rs1885120	MYH7B	0.06	1.39 (1.03-1.57)	.061	0.07	1.34	4.02×10^{-16}	Antonopoulou *et al.*, 2015
rs910873*	PIGU	0.07	1.30 (1.06-1.53)	.031	0.08	1.35	2.61×10^{-17}	Brown *et al.*, 2008
rs45430*	MX2	0.42	0.82 (0.67-0.97)	.008	0.4	0.89	8.80×10^{-8}	Barrett *et al.*, 2011
rs2284063	PLA2G6	0.37	0.92 (0.78-1.06)	.25	0.36	0.95	1.21×10^{-2}	Bishop *et al.*, 2009

CI, Confidence interval; *MAF*, minor allele frequency; *OR*, odds ratio; *SNP*, single-nucleotide polymorphism.
*Statistically significant ($P < .05$).

Supplemental Table IV. Sensitivity analysis for lifetime melanoma, adjusted for skin type, sunscreen, and latitude individually

Logistic model on lifetime melanoma (N = 3146, n cases = 112), adjust for skin type		
Variable	**OR (95%CI)**	***P* value**
Age (5-year)	1.09 (0.94-1.26)	.27
Skin Type (burn vs no burn)	1.81 (1.11-2.95)	.02
WGRS second tertile vs first tertile	1.42 (0.82-2.46)	.21
WGRS third tertile vs first tertile	2.64 (1.61-4.34)	<.01*
Logistic model on lifetime melanoma (N = 3146, n cases = 112), adjust for sunscreen		
Variable		
Age (5-year)	1.06 (0.91-1.23)	.44
Sunscreen (yes vs no)	2.27 (1.44-3.58)	<.01
WGRS second tertile vs first tertile	1.42 (0.82-2.46)	.21
WGRS third tertile vs first tertile	2.75 (1.66-4.45)	<.01*
Logistic model on lifetime melanoma (N = 3146, n cases = 112), adjust for latitude		
Variable		
Age (5-year)	1.05 (0.91-1.21)	.53
Latitude (Southern vs Northern)	1.39 (0.88-2.2)	.16
Latitude (Middle vs Northern)	1.46 (0.92-2.32)	.11
WGRS second tertile vs first tertile	1.47 (0.85-2.54)	.17
WGRS third tertile vs first tertile	2.92 (1.79-4.78)	<.01*

WGRS, Weight genetic risk score.
*Statistically significant ($P < .05$).

Supplemental Table V. Sensitivity analysis for incident melanoma, adjusted for skin type, sunscreen, and latitude individually

Survival model on incident melanoma (N = 3072, n cases = 38), adjust for skin type		
Variable	**HR (95% CI)**	***P* value**
Age (5-year)	0.98 (0.77-1.24)	.84
Skin type (burn vs no burn)	2.81 (1.04-7.57)	.05
WGRS second tertile vs first tertile	1.15 (0.44-2.97)	.78
WGRS third tertile vs first tertile	2.65 (1.17-6.01)	.02*
Survival model on incident melanoma (N = 3072, n cases = 38), adjust for sunscreen		
Variable		
Age (5-year)	0.93 (0.73-1.18)	.56
Sunscreen (yes vs. no)	2.96 (1.37-6.4)	.01
WGRS second tertile vs first tertile	1.14 (0.44-2.95)	.79
WGRS third tertile vs first tertile	2.72 (1.2-6.16)	.02*
Survival model on incident melanoma (N = 3072, n cases = 38), adjust for latitude		
Variable		
Age (5-year)	0.93 (0.74-1.18)	.55
Latitude (Southern vs Northern)	1.05 (0.49-2.24)	.90
Latitude (Middle vs Northern)	1.07 (0.49-2.35)	.86
WGRS second tertile vs first tertile	1.19 (0.46-3.09)	.72
WGRS third tertile vs first tertile	3.00 (1.33-6.78)	.01*

WGRS, Weight genetic risk score.
*Statistically significant ($P < .05$).

Supplemental Table VI. The harmonization/imputation effort involving 6 genome-wide association studies

	WHI study* (no.)					
	Hip fracture GWAS (BA3)	SHARe (M5)	GARNET (M13)	WHIMS+ (W63)	GECCO (AS224)	MOPMAP (AS264)
Directly genotyped GWAS data on dbGaP	No	Yes	Yes	Data uploaded to dbGaP June 2013	No	No
Study that funded GWAS	WHI-BAA3 (NHLBI)	NHLBI	WHI-GARNET (NHGRI)	NHLBI	WHI-AS224 (NCI)	WHI-AS264 (NIEHS and UNC)
GWAS platform	Illumina 550K and 610K	Affymetrix 6.0	Illumina HumanOmni1-Quad v1-0 B	HumanOmniExpress Exome-8v1_B	Illumina 610 and Cytochip 370K	Affymetrix Gene Titan, Axiom genome-wide human CEU I array plate
Design	Case-control	Cohort	Case-control (4 case groups)	Cohort	Case-control	Case-control
Phenotype for cases	Hip fracture	N/A	Type 2 diabetes, myocardial infarction, stroke, and venous thrombosis	N/A	Colorectal cancer	Ventricular ectopy (ever)
Other sample details	N/A	Minorities	Hormone therapy clinical trial	Hormone therapy clinical trial	N/A	Controls selected within centers, years, seasons and visit years in which cases originated
Ethnicity	Mostly white	African American and Hispanic	Mostly white	White	White	White
Sample size†	3690	11,992	4883	5687	2493	3069

GARNET, Genomics and Randomized Trials Network; *GECCO*, Genetics and Epidemiology of Colorectal Cancer Consortium; *GWAS*, genome-wide association study; *MOPMAP*, Modification of Particulate Matter—Mediated Arrhythmogenesis in Populations; *N/A*, not applicable; *NCI*, National Cancer Institute; *NHGRI*, National Human Genome Research Institute; *NHLBI*, National Heart, Lung, and Blood Institute; *NIEHS*, National Institute of Environmental Health Sciences; *SHARe*, Single-Nucleotide Polymorphism Health Association Resource; *SNP*, single-nucleotide polymorphism; *UNC*, University of North Carolina; *WHIMS*, Women's Health Initiative Memory Study.

*For some of the data files, these two platforms are considered different studies.

†The sample sizes are the number of samples after QC. Note that there are some subjects that are in multiple studies, as detailed herein.

Supplemental Table VII. Quality control parameters used for each of the genome-wide association studies

	Hip fracture GWAS	SHARe	GARNET	WHIMS+	GECCO	MOPMAP
Minimal sample call rate, %	98	95	98	97	97	95
Minimal SNP call rate, %	98	90	98	98	98	90
Hardy–Weinberg *P* value cutoff below which SNPs are excluded	1^{e-4}	1^{e-6}	1^{e-4}	1^{e-4}	1^{e-4}	1^{e-6}
Samples used for Hardy–Weinberg calculations	Controls of European ancestry	All samples, separate for Hispanics and African Americans	Unrelated controls of European ancestry	All	Controls	All
Minimum allele frequency cutoff, %	1	1	None	1	5	0.5

GARNET, Genomics and Randomized Trials Network; *GECCO*, Genetics and Epidemiology of Colorectal Cancer Consortium; *GWAS*, genome-wide association study; *MOPMAP*, Modification of Particulate Matter–Mediated Arrhythmogenesis in Populations; *SHARe*, Single-Nucleotide Polymorphism Health Association Resource; *SNP*, single-nucleotide polymorphism; *WHIMS*, Women's Health Initiative Memory Study.