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## Red meat and processed meat intake and risk of cutaneous melanoma in white women and men: Two prospective cohort studies

Hsi Yen, MD, MPH<sup>1,2,3</sup>, Wen-Qing Li, PhD<sup>4,5</sup>, Ashar Dhana, MBCh, MPH<sup>1,6</sup>, Tricia Li, MS<sup>7</sup>, Abrar Qureshi, MD, MPH<sup>4,5,7</sup>, and Eunyoung Cho, ScD<sup>4,5,7</sup>

<sup>1</sup>Harvard T.H. Chan School of Public Health, Boston, MA, U.S.A.

<sup>2</sup>Department of Dermatology, Chang Gung Memorial Hospital Linkou and Taipei Branch, Taoyuan, Taiwan

<sup>3</sup>College of Medicine, Chang Gung University, Taoyuan, Taiwan

<sup>4</sup>Department of Dermatology, Warren Alpert Medical School, Brown University, Providence, RI, U.S.A.

<sup>5</sup>Department of Epidemiology, Brown University School of Public Health, Providence, RI, U.S.A.

<sup>6</sup>Division of Dermatology, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa

<sup>7</sup>Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, U.S.A.

### Abstract

**Background:** Red and processed meat consumption has been associated with increased risk of several cancers, but association with cutaneous melanoma risk has been inconclusive.

**Objective:** To investigate the association between red and processed meat intake and melanoma risk.

**Methods:** Dietary information was assessed using food frequency questionnaires in two prospective cohorts - 75,263 women from the Nurses' Health Study (1984 – 2010) and 48,523 men from the Health Professionals Follow-up Study (1986 – 2010). Melanoma cases were confirmed by review of pathological records. Pooled multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models.

**Results:** A total of 679 female and 639 male melanoma cases were documented during follow-up. Red and processed meat intake was inversely associated with melanoma risk ( $P$  for trend =

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**Correspondence** Eunyoung Cho, Department of Dermatology, Warren Alpert Medical School, Brown University, Box G-D, Providence, RI 02912, Tel: 401-863-5895, Fax:401-863-5799, eunyoung\_cho@brown.edu.

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0.002); the pooled HRs (95% CIs) of the two cohorts were 1.00 (reference), 1.00 (0.87 – 1.14), 0.98 (0.86 – 1.13), 0.89 (0.77 – 1.02), and 0.81 (0.70 – 0.95) for increasing quintiles of intake.

**Limitations:** Findings may have limited generalizability, as the cohorts were limited to white health professionals.

**Conclusion:** Red and processed meat intake was inversely associated with melanoma risk in these two cohorts.

### Keywords

cutaneous melanoma; skin cancer; red meat; processed meat; prospective cohort study

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## BACKGROUND

Red meat is mammalian muscle meat that includes beef, pork, lamb, veal, and mutton.<sup>1</sup> Both meat processing and cooking can result in the formation of carcinogenic chemicals such as N-nitroso-compounds, polycyclic aromatic hydrocarbons, or heterocyclic aromatic amines.<sup>2, 3</sup> The World Health Organization's International Agency for Research on Cancer (IARC) classified consumption of processed meat as carcinogenic and red meat as probably carcinogenic, and concluded that processed meat is associated with increased risk in colorectal and possibly stomach cancer while red meat is potentially associated with increased risk in pancreatic and prostate cancer.<sup>1</sup>

Melanoma accounts for the majority of skin cancer deaths, and the rate of melanoma has risen in the U.S. over the last 30 years.<sup>4</sup> Despite the evidence of red and processed meat being associated with risk of other cancers,<sup>1</sup> the association between intake of red and processed meat and risk of cutaneous melanoma has been limited and inconclusive based on prior studies, which reported positive,<sup>5</sup> inverse,<sup>6</sup> or null associations.<sup>7, 8</sup> Therefore, we examined the association between red and processed meat intake and risk of incident melanoma in two prospective cohorts: the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS).

## METHODS

### Study Population

Established in 1976, the NHS enrolled 121,700 U.S. female registered nurses aged 30 to 55 years to answer a baseline questionnaire regarding their lifestyle and medical history. The HPFS was established in 1986, enrolling 51,529 U.S. male health professionals aged 40 to 75 years to answer a similar baseline questionnaire. These two cohorts and the validity of questionnaire results regarding disease outcome have been described elsewhere.<sup>9-11</sup> A food frequency questionnaire (FFQ) was used beginning in 1984 for NHS and then collected at four-year intervals between 1986 and 2010, while a similar FFQ for HPFS was introduced in 1986. Response rates generally exceed 90% for both cohorts.

Exclusion criteria of this analysis included study participants with missing information on red and processed meat intake at baseline FFQ (1984 in NHS and 1986 in HPFS), non-white participants, and prior history of any cancer except non-melanoma skin cancer (NMSC),

which may significantly alter a study participant's dietary habit and potentially introduce misclassification of red meat intake. Study participants with mucosal or acral melanomas were excluded from site-specific analysis due to potential heterogeneous etiologies. Melanoma in situ restricted to the epidermis were censored at the time of diagnosis, as melanoma in situ cases are not followed further in the cohorts and have distinct clinical implications with regards to management and prognosis compared to invasive melanoma cases. After these exclusions, data from 123,786 study participants (75,263 women and 48,523 men) were available for analysis. This study was approved by the institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health. The completion of self-administered questionnaire was interpreted as implying informed consent.

### **Dietary Assessment**

A semi-quantitative FFQ assessed average food intake over the previous year in both NHS and HPFS. Study participants chose from nine intake frequency responses, ranging from "never" to "more than 6 times a day." Red meat included: "hamburger," "beef, pork, or lamb as a sandwich or mixed dish," "beef, pork, or lamb as a main dish," and "liver." Processed meat included: "hot dogs," "bacon," and "other processed meats (sausage, salami, bologna, etc.)." Other dietary intake information for total energy (caloric intake), alcohol, coffee, and citrus (sum of grapefruit, orange, and grapefruit and orange juices) were also available. Our FFQ has been shown to be reproducible and provide a useful measure of intake over a one-year period in previous validation studies when compared to dietary records for both NHS and HPFS.<sup>12, 13</sup> Specifically, the correlation coefficients were mostly higher than 0.5 for individual red meat items after correction for attenuation due to random within-person variation in dietary records for NHS<sup>14</sup> and also higher than 0.5 for red and processed meats for HPFS.<sup>15, 16</sup>

### **Assessment of Other Covariates**

Information regarding host factors (family history of melanoma, natural hair color, number of arm moles, sunburn susceptibility as child or adolescent, number of lifetime blistering sunburns, and type of tan after repeated sun exposure as a child or adolescent), lifestyle factors (body mass index [BMI], physical activity level, and smoking), and environmental factors (cumulative ultraviolet [UV] flux since baseline) were collected in the cohorts.

### **Assessment of Melanoma**

Participants were asked about diagnosis of melanoma in each biennial questionnaire. Permission was acquired from these participants to verify the diagnoses through pathological reports. Tumor stage, location, and Breslow thickness were obtained if available. Invasive melanoma, defined as cancer invading beyond the epidermis, were further categorized into two subgroups according to sun exposure of tumor location: tumors on body sites with higher continuous sun exposure (head, neck, and extremities) and tumors on body sites with lower continuous sun exposure (truncal, shoulder, back, hip, abdomen, and chest).

## Statistical Analyses

Study participants contributed person-time beginning from the return of baseline questionnaire (1984 for NHS and 1986 for HPFS) until melanoma diagnosis, diagnosis of any other cancer except NMSC, death, loss to follow-up, or end of follow-up (June 2010 for NHS or January 2010 for HPFS), whichever came first. A cumulative average intake of dietary variables was utilized for statistical analysis, where melanoma incidence within each 2-year questionnaire cycle was related to the mean of red meat intake calculated from all preceding FFQs; this minimized measurement error in reporting dietary intake and best reflects long-term diet.<sup>17</sup> A model based on red meat consumption at baseline was also analyzed for sensitivity analysis.

A Cox proportional hazards regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between red and processed meat and risk of melanoma. Red and processed meat intake was divided into quintiles, with the lowest quintile as reference. Red and processed meat was further subcategorized into red meat and processed meat, and their association with melanoma risk analyzed separately. The following specific meat items were also analyzed: “hot dogs,” “bacon,” “hamburger,” “beef, pork, or lamb as a sandwich or mixed dish intake,” “beef, pork, or lamb as a main dish intake,” and “other processed meats (sausage, salami, bologna, etc.).” The association between red meat and melanoma were analyzed separately for NHS and HPFS. Multivariable analysis adjusted for other potential confounders identified in previous studies to be associated with melanoma.<sup>18–24</sup>

Analyses was also stratified by potential effect modifiers, including number of arm moles, sunburn susceptibility as child or adolescent, annual UV flux at residence, BMI, physical activity level, smoking status, alcohol intake, and by personal history of cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), as a previous study identified increased risk of melanoma after developing NMSC.<sup>25</sup> Stratified analysis by Breslow thickness of tumor (below and above median) and body site of melanoma (high and low sun exposure site) were also evaluated.

Results from NHS and HPFS were pooled and summary estimates were generated using random-effect models.<sup>26</sup> *P* value for heterogeneity was assessed using the *Q* statistic. Tests of trend were performed by using median values for each quintile and treating this variable as a continuous variable in the regression model. A metaregression model was used to test for variation in relative risks by other potential modifying factors.<sup>27</sup> Lag analyses was done by excluding the first 4 years of follow-up to address possibility of reverse causality and explore temporal relation. All statistical analysis was carried out using Statistical Analytic Systems software (version 9.4; SAS Institute, NC). All statistical tests were two-sided with *P* value < 0.05 considered statistically significant.

## RESULTS

At baseline, both women and men with higher red and processed meat intake were more likely to have higher BMI, lower physical activity level, smoke cigarettes, have higher caloric intake, and drink coffee (**Supplemental Table I**). Men with higher red and processed

meat intake were also more likely to drink alcohol. There was no obvious difference in other host or sun-related factors across red and processed meat intake quintiles for both men and women.

A total of 1,318 incident invasive melanomas were documented over 2.6 million person-years of follow-up (NHS: 679 cases and 1,698,571 person-years; HPFS: 639 cases and 924,597 person-years). Total intake of red and processed meat was inversely associated with risk of incident melanoma, and the association did not differ appreciably between age-adjusted and multivariable models (**Supplemental Table II**). The association appeared similar for NHS and HPFS ( $P$  for heterogeneity  $> 0.99$  when comparing highest to lowest quintile of intake). After pooling the two cohorts, the pooled multivariable HRs (95% CIs) were 1.00 (reference), 1.00 (0.87 – 1.14), 0.98 (0.86 – 1.13), 0.89 (0.77 – 1.02), and 0.81 (0.70 – 0.95), respectively, for increasing quintiles of red and processed meat intake ( $P$  for trend = 0.002), suggesting a dose-dependent inverse association between red and processed meat and cutaneous melanoma risk. Inverse associations with risk of melanoma were consistent, although not significant, when red meat and processed meat were examined separately, with the pooled HR (95% CI) 0.86 (0.65 – 1.14) for red meat and 0.83 (95% CI 0.69 – 1.00) for processed meat comparing highest to lowest quintile of intake. Sensitivity analysis based on the baseline intake of red and processed meat yielded similar findings (data not shown). Lag analyses suggested that the associations between red and processed meat and melanoma risk were generally consistent to those from the main analyses (data not shown).

The analyses of specific red and processed meat items (**Supplemental Table III**) found significant inverse association when comparing highest to lowest quintile intake for “hot dogs” (HR = 0.77, 95% CI 0.60 – 0.99;  $P$  for trend = 0.30) and “beef, pork, or lamb as a sandwich or mixed dish” (HR = 0.69, 95% CI 0.53 – 0.89;  $P$  for trend = 0.06) with risk of melanoma in women.

The analyses by body location and Breslow thickness of melanoma found that the inverse association between red and processed meat intake and melanoma risk was more evident and significant to melanoma at low sun exposure sites (pooled HR = 0.63, 95% CI 0.43 – 0.91 when comparing highest to lowest quintile;  $P$  for trend = 0.02) (**Supplemental Table IV**) and melanoma with thinner Breslow thickness (median = 0.60 mm in women; median = 0.67 mm in men) (pooled HR = 0.74, 95% CI 0.56 – 0.99 when comparing highest to lowest quintile;  $P$  for trend = 0.009) (**Supplemental Table V**).

We also found significant effect modification by sunburn susceptibility as a child or adolescent ( $P$  for interaction = 0.01) and by personal history of NMSC ( $P$  for interaction = 0.02). Significant inverse association between red and processed meat intake and melanoma risk was only observed among participants with more severe sunburn reactions as a child or adolescent (HR = 0.65, 95% CI 0.43 – 0.96 when comparing highest to lowest quintile;  $P$  for trend = 0.01), and those without personal history of NMSC (HR = 0.74, 95% CI 0.58 – 0.95 when comparing highest to lowest quintile;  $P$  for trend = 0.002) (**Supplemental Table V**). There was no evidence that the association between red and processed meat intake and melanoma risk was modified by other melanoma risk factors including number of arm

moles, annual UV flux, BMI, physical activity level, smoking status, or alcohol intake (*P* for interaction > 0.61 for these factors).

## DISCUSSION

The pooled results from these two prospective cohort studies found that red and processed meat intake was not positively associated with risk of cutaneous melanoma, after adjusting for other known melanoma risk factors and potential confounders. Study participants with the highest quintile of total red and processed meat intake had a 19% lower risk compared to those with the lowest quintile of intake. The associations were generally similar, although largely not significant, for red meat and processed meat as well as for specific meat items.

There have been few epidemiological studies investigating red and processed meat intake and its association with melanoma risk. Our results are similar to a prospective cohort study including 1,531 melanoma cases, which reported associations for red meat (multivariable HR = 0.95, 95% CI 0.81 – 1.11) and processed meat (multivariable HR = 0.82, 95% CI 0.71 – 0.96) when comparing highest to lowest quintile of intake.<sup>6</sup> Of note, melanoma was one of the few cancer sites that suggested an inverse direction of association in that study. However, a case-control study of 249 melanoma cases with tumors more than 1 mm thick found a multivariable hazard rate of 1.93 (95% CI 1.08 – 3.45) comparing weekly or more to less than weekly red meat intake.<sup>5</sup> Two other case-control studies including 278 cases and 59 cases found null association between red meat intake and melanoma,<sup>7, 8</sup> but these studies were limited by small study size.

There may be some components in red and processed meat which may be beneficial against melanoma. Red meat contains retinol,<sup>28</sup> which was shown to have an inhibitory effect on tumor promotion<sup>29</sup> and reduce melanoma risk<sup>30,31</sup>. However, retinol intake was not associated with melanoma risk in a pooled analysis of NHS and Nurses' Health Study II, another cohort study of women.<sup>32</sup> Red meat is also a main source of nicotinamide,<sup>33</sup> a niacin derivative, which has been shown to be immunoprotective against UV radiation<sup>34</sup> and reduce rates of skin cancers.<sup>35</sup> However, niacin intake was not associated with melanoma in the cohorts.<sup>36</sup>

The inverse association between red and processed meat intake and melanoma was limited to those with severe sunburn reactions as a child or adolescent. While higher levels of sunlight exposure and severity of sunburn in childhood are strong determinants of melanoma,<sup>37, 38</sup> it remains to be clarified if red meat plays a significant role during childhood or adolescence in determining melanoma risk. On the other hand, analyses by body site found significant inverse association between red and processed meat intake and melanoma at low sun exposure sites only, but not for those at high sun exposure sites, highlighting UV exposure as a major melanoma risk factor that may outweigh the modest protective effect of red and processed meat intake. Also, those without history of NSMC had significant inverse association between red and processed meat intake and melanoma risk. Whether red and processed meat consumption plays a differing role in NMSC compared to melanoma should be addressed in future studies with NMSC as a primary outcome.

The strengths of this study include a prospective design with large sample size, long follow-up duration, multiple assessments of red meat intake, and analysis that adjusted for a number of potential confounders. In addition, cumulative averaged red and processed meat intake may more accurately reflect long-term dietary habits by minimizing within-person random error. Furthermore, the two cohorts are comprised of mainly white educated U.S. health professionals, reducing potential confounding due to socioeconomic status or ethnicity. At the same time, this presents a limitation due to potential restricted generalizability.

In summary, our pooled analysis of two large cohorts of white health professionals indicated that higher red and processed meat intake had a modest inverse association with melanoma risk. However, processed meat intake is carcinogenic and red meat intake has been associated with risk of other cancers other than melanoma,<sup>1</sup> as well as increased mortality.<sup>39, 40</sup> Therefore, our findings need to be replicated in other populations, and should not lead to a dietary recommendation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

|             |   |
|-------------|---|
| <b>HR</b>   | hazard ratio                                |
| <b>CI</b>   | confidence interval                         |
| <b>IARC</b> | International Agency for Research on Cancer |
| <b>NHS</b>  | Nurses' Health Study                        |
| <b>HPFS</b> | Health Professional Follow-up Study         |
| <b>FFQ</b>  | food frequency questionnaire                |
| <b>NMSC</b> | non-melanoma skin                           |
| <b>BMI</b>  | body mass index                             |
| <b>UV</b>   | ultraviolet                                 |
| <b>SCC</b>  | squamous cell carcinoma                     |



**BCC** basal cell carcinoma

## CITATION

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**Capsule Summary**

- Epidemiological studies investigating red and processed meat intake and melanoma have been limited and inconclusive.
- We found an inverse association between red and processed meat intake and melanoma.
- Because processed meat and potentially red meat may contain carcinogens, our findings need to be replicated in other populations.

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