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Proposal for an annual skin examination by a general practitioner for patients at high risk for melanoma: A French cohort study.

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ABSTRACT

Objective: To evaluate patient participation in a targeted screening study for melanoma after receiving a mailed invitation to an annual skin examination by a general practitioner (GP). Deviations in the healthcare journey and the efficacy of the screening procedure were also analysed.

Methods: A prospective cohort study conducted in a primary care setting in western France. A total of 3,897 patients at elevated risk for melanoma (identified using the Self-Assessment of Melanoma Risk Score (SAMScore)) consented to participate in a targeted melanoma screening project in 2011. One year later, the participants were invited by mail to consult their GP for an annual skin examination. The assessment focused on participation (compared with the first year, including populations at risk for thick melanoma), on the healthcare journey, and on the incidence and thickness of melanomas diagnosed one year after the reminder. Clinical and pathological data were collected during the 12 months post-reminder and were analysed using SAS.

Results: Of the 3,745 patients who received the mailed invitation, 61.0% underwent a skin examination. Fewer patients were referred to a dermatologist than in the first year (12.2% vs. 38.3%, p<0.001), but the patients were more compliant when they were referred (68.8% vs. 59.1%, p=0.003). Six melanomas were diagnosed within one year post-reminder; therefore, the incidence of melanoma in the study population was 160/100,000. The participation of patients at risk for thick melanomas (any patient over 60 years and men over 50 years) was significantly greater than that of other subgroups (72.4% vs. 49.6%, p<0.001, and 66.0% vs. 52.4%, p<0.001, respectively).

Conclusion: This study confirms the benefits of developing a targeted screening strategy in primary care. In particular, after the annual reminder, patient participation and the

concentration effect of melanoma cases remained high in patients at elevated risk of thick melanomas.

Keywords: melanoma; screening; early detection of cancer; primary healthcare

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ARTICLE SUMMARY

Strengths and limitations of this study

- The study was conducted in a primary care setting.
- The study participants were recruited using a validated and reproducible procedure based on the Self-Assessment of Melanoma Risk Score.
- Six months after having received an annual reminder inviting them to consult their general practitioner for a targeted screening for melanoma, 61.0% of patients had underwent a skin examination.
- Although only six new melanomas were detected, these results yielded a crude melanoma incidence of 160/100,000 in the cohort population.
- The participation of patients at risk for thick melanoma was significantly above average.

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Competing interest statement

No financial disclosures were reported by the authors.

INTRODUCTION

In France, the incidence of melanoma is estimated at 10.8/100,000 in men and 11.0/100,000 in women [1]. Overall, the incidence increased by 3.5 between 1980 and 2012 [1]. Because the lesions are visible, they should be detected at the early stage through skin examination. However, in 2012, melanoma was responsible for 1,672 deaths in France [1]. The main prognostic factor is the Breslow thickness (in millimetres) at the time of the diagnosis [2]. The 5-year survival of patients with localised melanoma is 98.1% compared with only 16.1% in metastatic melanoma patients [3]. Despite these findings, routine screening through total skin examination is not recommended in France [4], the United States [5], Australia or New Zealand, although the last has the highest incidence in the world [6,7]. Indeed, the efficacy of routine screening in decreasing mortality has not been proven [5], and routine screening would be expensive to perform [8].

Identifying high-risk subjects could be a more valuable [9] and cost-effective strategy [8,10,11]. The main risk factors for melanoma are well identified [12–14]: a personal or family history of melanoma, a number of nevi greater than 40, the number of atypical nevi, phenotype I or II, freckles and actinic damage, and a history of sunburns. Certain demographic groups have also been identified as being at higher risk for *thick* melanoma [9,15]: men, individuals over 60 years [16,17], and men over 50 years [18].

A low physician density has also been associated with the identification of thicker melanomas [19–21]. Melanomas tend to be thinner when they are detected by physicians rather than patients and also when they are detected during a screening skin examination rather than during routine care [17,22–26]. However, only 20% of patients who have had melanoma report that they previously consulted a dermatologist [27]. Therefore, general practitioners (GPs) could play a significant role in this screening. One study has reported that the proportion of melanomas diagnosed by GPs in France increased from 24% in 2004

to 42% in 2008, following the implementation of a system requiring patients to register their attending physician [28].

Based on these findings, our team has developed a targeted melanoma screening procedure grounded in primary care, using the Self-Assessment of Melanoma Risk Score (SAMScore). This score is based on a 7-item self-administered questionnaire (Figure 1) that a patient can answer without specific medical knowledge (29-31), and allows for the selection of a population at high risk for melanoma during primary care consultations [29–32]. It was used to create a cohort of patients at high risk for melanoma (COPARIME) who were then asked to participate in a pilot targeted screening for melanoma (NCT01610531) [32]. The targeted melanoma screening procedure comprised 3 steps: (I) identifying high-risk patients, (II) asking GPs to perform a total skin examination on these high-risk patients, and (III) referring patients to a dermatologist if needed (for patients requiring a specialist opinion according to the GP). Between April and October 2011, 3,917 patients were included, and nine had melanoma. The crude incidence observed (229/100,000) highlights the potential benefit of such a targeted screening [32]. However, the assessment also had several limitations.

First, certain patients included in the screening seemed marginally concerned: 30% of them had not consulted a dermatologist, despite being referred [32,33]. Conversely, several patients had consulted a dermatologist without having been referred. Furthermore, GPs felt the need for a dermatologist's opinion for approximately 40% of patients, suggesting only modest efficacy of the GP consultation [32]. Finally, the observed incidence must be considered a cumulative incidence comprising the diagnosis of prevalent cases in the population during the first year, a common bias reported during occasional screening procedures.

One year after their inclusion in the targeted screening procedure, our team contacted all patients at risk for melanoma from the COPARIME cohort. They received a mailed invitation to reconsult their GP for an annual skin examination. The aim of this study was threefold: to assess the participation following this reminder, to evaluate deviations in the healthcare journey and to compare the efficacy of the procedure with that observed in the first year. An additional analysis focused on populations at risk for thick melanoma: men, older patients, and rural patients.

METHOD

Design of the study

This study was based on the prospective follow-up of the COPARIME cohort. The patients were initially enrolled between April 11 and October 30, 2011, by 78 GPs in western France, specifically in the departments of Loire-Atlantique and Vendée. All dermatologists in both departments participated in the study. The dermatologist density is 5.3/100,000 inhabitants in Loire-Atlantique, a predominantly urban department, and 2.1/100,000 inhabitants in Vendée, a more rural department. These physician densities are comparable to those of other French departments (national mean: 5.3/100,000) [34].

Participants

The eligibility criteria to receive the reminder at one year were as follows: being at high risk for melanoma according to the SAMScore, having agreed to participate in the targeted melanoma screening one year earlier, being over 18, and having no personal history of melanoma. Twenty patients were excluded from the COPARIME database either because

they had developed melanoma during the year since initially participating (9 patients) or because they had died (11 patients). As a result, a total of 3,897 patients were eligible (Figure 2).

Annual skin examination by the general practitioner

The invitation to reconsult their GP for an annual skin examination was sent to eligible patients by mail one year after their inclusion in the cohort.

The GP was asked to perform a total skin examination. Patients were referred to a dermatologist based on the opinion of the GP (as in routine care). For referred patients, dermatologists were asked to classify their examinations according to three categories: "benign lesion", "lesion to monitor" or "indication for exeresis". When exeresis was indicated, the last step was anatomopathological examination.

Data collection

While the reminder was sent to the patients, each GP received by mail a table summarising the following data to be collected for each patient: the date of skin examination, the identification or not of a suspicious lesion, and whether the patient was referred to a dermatologist. An updated table was sent to GPs at months 6 and 12. If data were missing one year after sending the reminder, an investigator contacted the GP by telephone and offered to visit the medical practice to facilitate data collection.

One year after the reminder was mailed to the last patient in the cohort, each dermatologist received a table by mail, summarising the data to be collected for each patient: the date of the dermatological consultation and conclusion derived from the skin examination:

"benign lesion", "lesion to monitor", or "indication for exeresis". The anatomopathological result was also recorded when available. If data were missing, an investigator contacted the dermatologist by telephone and offered to visit the medical practice.

Between June and December 2013, all patients for whom no data were available were recontacted to determine whether they had consulted a dermatologist. All of the data collected during these telephone calls with patients were then confirmed or invalidated based on data from a physician (GP or dermatologist).

All of the data were recorded in an Access database.

Assessment of participation, deviations in the healthcare journey and efficacy

Participation in the follow-up annual skin examination by the GP was assessed 6 months after mailing the invitation.

Deviations in the healthcare journey following the mailing of the invitation were analysed after patient classification into 6 categories: (I) attended the skin examination by the GP, as expected; (II) directly consulted a dermatologist, even though he/she had not consulted a dermatologist when his/her GP had referred him/her the previous year, but without reconsulting the GP at this time; (III) directly reconsulted his/her dermatologist as part of his/her dermatological follow-up; IV) directly reconsulted his/her dermatologist on his/her own initiative; (V) had no skin examination by his/her GP and no dermatological consultation; and (VI) referred to a dermatologist following examination by his/her GP but did not consult the dermatologist.

The efficacy of the procedure was described using the following data:

- the proportion of patients with a "benign lesion", "lesion to monitor", or "indication for exeresis", depending on whether the patient consulted a

dermatologist either as part of a specialised follow-up because he/she was referred by his/her GP or on his/her own initiative;

- the incidence and thickness of melanomas detected in the high-risk population after the reminder compared with after the first year of follow-up;
- the proportion of patients referred to a dermatologist by their GP and the proportion of patients who actually consulted a dermatologist compared with the proportion during the first year and among populations at risk for thick melanoma.

Statistical analysis

Quantitative data are presented as means and medians. Data from the first year were compared with data from the second year using the Chi-square and Fisher tests. Additionally, a subgroup analysis was performed for men, patients over 60 years, men over 50 years, and patients living in rural areas. The statistical significance was set at 0.05. R 3.10.0 software was used.

Opinion of the ethics committee

The ethics committee of Tours University Hospital has given its favourable opinion on the performance of the study (n°2011-R2-BRD 10/11-N).

RESULTS

Patient demographics

Of the 3,897 patients, 117 patients moved without leaving a forwarding address, and 35 discontinued their participation in the study. The healthcare journeys of 3,745 patients are

described (Figure 2). The patients' mean age was 44.5 (±15.6) years, and there were 1,197 (32%) men. In total, 713 (19%) patients were over 60 years of age, and 426 (11.3%) patients were men over 50 years. Finally, 2,427 (64.8%) patients lived in Loire-Atlantique; 1,206 (32.2%) in Vendée, and 112 (3.25%), in other departments.

Patient participation and deviations in the healthcare journey

After the one-year follow-up, 61% of the patients included in the targeted screening procedure reconsulted their GP, and 16% reconsulted a dermatologist (Figure 3). The mean delay between GP and dermatologist consultations was of 119 days. The mean delay between dermatologist consultation and exeresis was of 54 days.

Figure 2 shows the deviations in the healthcare journey 6 months after mailing the invitation to reconsult: 264 (7%) patients directly consulted a dermatologist, 2,021 (54%) patients reconsulted their GP, and 1,159 (31%) had no skin monitoring.

Efficacy of the screening

The clinical results of the dermatological consultations are presented in Table 1. While 83 patients underwent exeresis, 6 melanomas, 5 squamous cell carcinomas and 15 basal cell carcinomas were diagnosed. Of the 6 melanomas, 5 were identified among the patients initially referred by GPs.

The median thickness of melanomas detected during the second year was 0.405 mm (Table 2). One melanoma was greater than 1 mm thick; it was identified in a patient who had not consulted a dermatologist after having been referred the first year. In compliant patients,

the mean time between the skin examination by the GP and the exeresis was 349 days (Table 2).

Comparison with the first year and subgroup analysis

The proportion of patients referred to a dermatologist by GPs was lower after the reminder at one year than it was at the time of initial inclusion in the screening (12.2% vs. 38.3%, p<0.001) (Table 3). Moreover, the proportion of referred patients who actually consulted a dermatologist increased (68.8% vs. 59.1%, p<0.001), although the proportion of all patients who consulted a dermatologist was lower (15.8% vs. 23.9%, p<0.001). Additionally, the proportion of patients lost to follow-up increased (17.1% vs. 2.6%, p<0.001). The other data were not significantly different between the first and the second years of follow-up.

The subgroup analysis yielded the following results: (1) in men over 50 years, the proportion of patients compliant with the GP consultation (66.0% vs. 52.4%, p<0.001), the exeresis rate (21.0% vs. 11.6%, p=0.029) and the number of malignant lesions identified after exeresis (66.7% vs. 21.5%, p<0.001) were higher when compared with the reference group; (2) in patients over 60 years, the proportion of patients compliant with the GP consultation (72.4% vs. 49.6%, p<0.001) and the number of malignant lesions identified after exeresis (66.7% vs. 19.4%, p<0.001) were higher when compared with the reference group.

The incidence of melanoma standardised to the populations of both departments was $183.7/10^5$ for men and $98.7/10^5$ for women.

DISCUSSION

Main results

Six months after having received the annual reminder inviting them to schedule a total skin examination with their GP, 61.0% of patients underwent a skin examination. Among these patients, 7.1% directly consulted a dermatologist. Among patients who consulted their GP, 12.2% were referred to a specialist. Six new melanomas were detected, corresponding to a crude incidence of 160/100,000. The participation of populations at risk for thick melanoma was significantly above average.

Strengths and weaknesses

The strengths of this study are the size of the study population, the screening procedure initiated under primary care and in real care conditions, the use of a single validated and reproducible tool to detect high-risk subjects, and the prospective follow-up of the cohort.

This study also has certain limitations, including the number of patients lost to follow-up, the inclusion bias (with a population in which women and young subjects were over-represented) and the absence of data on the false negatives of the procedure. Female over-representation is usually found in skin screening programs [35–38] and more generally in cancer screening [39,40]. This bias could also be related to the population seeking consultation in general practice, which is not entirely representative of the general population [32,41].

Interpretation of the results and comparison with data from the literature

The 61.0% rate of participation in the annual skin examination is higher than that observed for other cancers in France: 52.1% for mammography [42], 34.3% for Hemoccult II [43]

and 58.7% for cervical smear [44]. This good participation, observed after the one-year reminder, is a significant result that indicates the success of the screening. Offering a targeted screening, rather than a screening of the general population, could be associated with better participation.

Six melanomas with a median Breslow thickness of 0.405 mm were diagnosed during the second year of the follow-up and only one melanoma was greater than 1 mm thick. Similarly, other authors have reported that screening procedures help in identifying predominantly thin lesions with a median Breslow thickness of approximately 0.3 mm [31,45,46].

The standardised incidence of melanoma in the high-risk population in this study was much higher than the incidence known in this geographic area, or 7.9 and 3.7 times higher for men and women, respectively. This increased incidence confirms that identifying patients at elevated risk of melanoma is relevant. This result is novel because most studies have only reported the benefit of a screening procedure immediately after the intervention. The observation of transient over-detection in these studies did not allow for an assessment of the benefit that would have been obtained if the screening procedure had been extended [31,32,47].

No very thick melanomas (> 3mm) were diagnosed in our high-risk population over the course of two years. The study does not allow us to conclude whether this result is due to the efficacy of the screening procedure or if it is simply related to the low incidence of thick melanomas in the population. However, the only melanoma greater than 1 mm was paradoxically detected during the second year. The corresponding patient had been referred to a dermatologist during the first year, but he consulted the dermatologist more than one year later. For this type of minimally compliant patient, our mail could have served as a reminder that was responsible for any appointment made. Thus, the benefits of

a primary care-based targeted screening on the incidence of very thick melanomas could be due to not only the involvement of GPs trained in screening (54) but also the impact of a simple annual reminder on minimally compliant patients.

In total, 95 patients consulted a dermatologist on their own initiative, and one of these patients had a melanoma. This finding is consistent with the results of other studies that have shown that certain subjects participating in skin screening programs appropriately pursued consultations on their own [35,47–50]. In our study, it is likely that patients who were sensitised to their risk status and educated in skin self-examination by their GP directly consulted a dermatologist when they identified a suspicious lesion. Indeed, the impact of a screening procedure on skin self-examination practices has been shown previously [51]. This phenomenon of spontaneous screening was also highlighted in a pilot study that led to systematised skin screening in Germany [35]; although the participation rate in this german study was only 19%, the screening program led to the diagnosis of one in two melanomas listed on the cancer registry.

The present study shows that the importance of deviations in the healthcare journey does not lessen the importance of the GP consultation. First, 5 of the 6 new melanoma cases were identified among patients referred by their GP. Second, the effect of the concentration related to the GP consultation increased. Indeed, the proportion of patients referred to a dermatologist by their GP decreased in the second year compared with the first year (12.2% vs. 38.3%). This proportion is more consistent with previously published data that have revealed proportions of referred patients ranging between 7.4% and 26% [35,52–54]. This evolution could be explained by the GP's need to perform a reference examination in the year of inclusion, whereas his/her role would subsequently be to ensure the absence of evolution of pre-existing lesions.

The benefit of the proposed screening seemed highest in populations at risk for thick melanoma. Although only 32% of the cohort was male, 11.3% was composed of men over 50 years and 19% was composed of subjects over 60 years, these populations accounted for 50%, 33% and 50% of melanoma patients, respectively, confirming that the efficacy of melanoma screening is high in these populations [18,53,55]. In the context of such screening, the challenge would be to identify those patients who do not consult spontaneously. One solution would be to develop policies focused on primary care to reduce health inequalities in the field of prevention [56,57].

Practical implications and perspectives

More than half of the patients identified as being at risk for melanoma using the SAMScore responded positively to our mailing about scheduling an annual skin examination with their GP. The high melanoma incidence and the low melanoma thickness found both confirm the value of a targeted screening conducted in primary care.

Extending the follow-up of our cohort would allow for an assessment of the proportion of false negatives related to the GP's examination. Other major issues include assessing the follow-up pace to be proposed in this population and the related costs. The assessment of a beneficial effect on mortality will require a randomised study.

Ethical approval

The ethics committee of the University Hospital of Tours approved this study (n° 2011-R2-BRD 10/11-N).

AUTHORS' CONTRIBUTIONS

CR conceived of the study, participated in its design and supervision, was responsible for the GP network, and was responsible for drafting the manuscript. CG participated in the design of the study, was responsible for the data collection, and helped to draft the manuscript. GQ participated in the design of the study, controlled the pathological reports, and helped to draft the manuscript. MD participated in the data collection and helped to draft the manuscript. AG performed the statistical analysis and helped to draft the manuscript. AK and BD participated in the design, were responsible for the dermatologist network, and provided administrative or technical support. JMN participated in the design of the study, was responsible for the statistical analysis, was responsible for study supervision and helped to draft the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1 Binder-Foucard F, Belot A, Delafosse P, et al. Estimation nationale de l'incidence et de la mortalité par cancer en France entre 1980 et 2012. Partie 1 - Tumeurs solides. Saint-Maurice (Fra): Institut de Veille Sanitaire 2013.

2 Balch CM, Gershenwald JE, Soong S-J, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol Off J Am Soc Clin Oncol 2009;**27**:6199–206. doi:10.1200/JCO.2009.23.4799

3 How Many People Survive 5 Years Or More after Being Diagnosed with Melanoma of the Skin? http://seer.cancer.gov/statfacts/html/melan.html#survival (accessed 10 Sep2014).

4 Haute Autorité de Santé. Stratégie de diagnostic précoce du mélanome. 2006.www.has-sante.fr/

5 U.S. Preventive Services Task Force. Screening for skin cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009;**150**:188–93.

6 Cancer Council Australia, New Zealand, Ministry of Health, et al. Clinical practice guidelines for the management of melanoma in Australia and New Zealand: evidence-based best practice guidelines. Sydney, N.S.W.; New Zealand: : Cancer Council Australia : Australia Cancer Network ; Ministry of Health 2008.

7 Bray F, Ren J-S, Masuyer E, et al. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 2013;**132**:1133–45. doi:10.1002/ijc.27711

8 Losina E, Walensky RP, Geller A, et al. Visual screening for malignant melanoma: a cost-effectiveness analysis. Arch Dermatol 2007;**143**:21–8. doi:10.1001/archderm.143.1.21

9 Curiel-Lewandrowski C, Chen SC, Swetter SM, et al. Screening and prevention measures for melanoma: is there a survival advantage? Curr Oncol Rep 2012;**14**:458–67. doi:10.1007/s11912-012-0256-6

10 Freedberg KA, Geller AC, Miller DR, et al. Screening for malignant melanoma: A cost-effectiveness analysis. J Am Acad Dermatol 1999;**41**:738–45.

11 Gordon LG, Rowell D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP Published Online First: 2 August 2014. doi:10.1097/CEJ.0000000000000056

12 Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur J Cancer Oxf Engl 1990 2005;**41**:28–44. doi:10.1016/j.ejca.2004.10.015

13 Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer Oxf Engl 1990 2005;**41**:45–60. doi:10.1016/j.ejca.2004.10.016

14 Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur J Cancer Oxf Engl 1990 2005;**41**:2040–59. doi:10.1016/j.ejca.2005.03.034

15 Geller AC, Swetter SM, Oliveria S, et al. Reducing mortality in individuals at high risk for advanced melanoma through education and screening. J Am Acad Dermatol 2011;**65**:S87–94. doi:10.1016/j.jaad.2011.05.045

16 Geller AC, Elwood M, Swetter SM, et al. Factors related to the presentation of thin and thick nodular melanoma from a population-based cancer registry in Queensland Australia. Cancer 2009;**115**:1318–27. doi:10.1002/cncr.24162

17 Swetter SM, Pollitt RA, Johnson TM, et al. Behavioral determinants of successful early melanoma detection: role of self and physician skin examination. Cancer 2012;**118**:3725–34. doi:10.1002/cncr.26707

18 Geller AC, Sober AJ, Zhang Z, et al. Strategies for improving melanoma education and screening for men age >or= 50 years: findings from the American Academy of Dermatological National Skin Cancer Sreening Program. Cancer 2002;**95**:1554–61. doi:10.1002/cncr.10855

19 Van Durme DJ, Ullman R, Campbell RJ, et al. Effects of physician supply on melanoma incidence and mortality in Florida. South Med J 2003;**96**:656–60. doi:10.1097/01.SMJ.0000053569.81565.19

20 Stitzenberg KB, Thomas NE, Dalton K, et al. Distance to diagnosing provider as a measure of access for patients with melanoma. Arch Dermatol 2007;**143**:991–8. doi:10.1001/archderm.143.8.991

21 Aneja S, Aneja S, Bordeaux JS. Association of increased dermatologist density with lower melanoma mortality. Arch Dermatol 2012;**148**:174–8. doi:10.1001/archdermatol.2011.345

22 Helfand M, Mahon SM, Eden KB, et al. Screening for skin cancer. Am J Prev Med 2001;**20**:47–58. doi:10.1016/S0749-3797(01)00258-6

23 Epstein DS, Lange JR, Gruber SB, et al. Is physician detection associated with thinner melanomas? JAMA J Am Med Assoc 1999;**281**:640–3.

24 McPherson M, Elwood M, English DR, et al. Presentation and detection of invasive melanoma in a high-risk population. J Am Acad Dermatol 2006;**54**:783–92. doi:10.1016/j.jaad.2005.08.065

25 Aitken JF, Elwood M, Baade PD, et al. Clinical whole-body skin examination reduces the incidence of thick melanomas. Int J Cancer J Int Cancer 2010;**126**:450–8. doi:10.1002/ijc.24747

26 Richard MA, Grob JJ, Avril MF, et al. Delays in diagnosis and melanoma prognosis (II): the role of doctors. Int J Cancer J Int Cancer 2000;**89**:280–5.

27 Geller AC, Koh HK, Miller DR, et al. Use of health services before the diagnosis of melanoma: implications for early detection and screening. J Gen Intern Med 1992;**7**:154–7.

28 Grange F, Barbe C, Mas L, et al. The role of general practitioners in diagnosis of cutaneous melanoma: a population-based study in France. Br J Dermatol 2012;**167**:1351–9. doi:10.1111/j.1365-2133.2012.11178.x

29 Quéreux G, Nguyen J-M, Volteau C, et al. Creation and test of a questionnaire for self-assessment of melanoma risk factors: Eur J Cancer Prev 2010;**19**:48–54. doi:10.1097/CEJ.0b013e328333d113

30 Quéreux G, Moyse D, Lequeux Y, et al. Development of an individual score for melanoma risk: Eur J Cancer Prev 2011;**20**:217–24. doi:10.1097/CEJ.0b013e32834474ae

31 Quéreux G, N'guyen J-M, Cary M, et al. Validation of the Self-Assessment of Melanoma Risk Score for a melanoma-targeted screening. Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP 2012;**21**:588–95. doi:10.1097/CEJ.0b013e328353ed68

32 Rat C, Quereux G, Grimault C, et al. Melanoma incidence and patient compliance in a targeted melanoma screening intervention. One-year follow-up in a large French cohort of high-risk patients. Eur J Gen Pract 2014:1–7. doi:10.3109/13814788.2014.949669

33 Rat C, Quereux G, Monegier du Sorbier M, et al. Patients at elevated risk of melanoma: individual predictors of non-compliance to GP referral for a dermatologist consultation. Prev Med 2014;**64**:48–53. doi:10.1016/j.ypmed.2014.03.029

34 Démographie médicale interactive | Démographie médicale. Cons. Natl. Médecins. http://demographie.medecin.fr/demographie (accessed 13 Sep2014).

35 Breitbart EW, Waldmann A, Nolte S, et al. Systematic skin cancer screening in Northern Germany. J Am Acad Dermatol 2012;**66**:201–11. doi:10.1016/j.jaad.2010.11.016

36 Andrulonis R, Secrest AM, McGuire ST, et al. The influence of age and sex on reasons for seeking and expected benefits of skin cancer screening. Arch Dermatol 2010;**146**:1097–102. doi:10.1001/archdermatol.2010.254

37 De Rooij MJ, Rampen FH, Schouten LJ, et al. Factors influencing participation among melanoma screening attenders. Acta Derm Venereol 1997;**77**:467–70.

38 Argenziano G, Zalaudek I, Hofmann-Wellenhof R, et al. Total body skin examination for skin cancer screening in patients with focused symptoms. J Am Acad Dermatol 2012;**66**:212–9. doi:10.1016/j.jaad.2010.12.039

39 Davis JL, Buchanan KL, Katz RV, et al. Gender differences in cancer screening beliefs, behaviors, and willingness to participate: implications for health promotion. Am J Mens Health 2012;**6**:211–7. doi:10.1177/1557988311425853

40 Sach TH, Whynes DK. Men and women: beliefs about cancer and about screening. BMC Public Health 2009;**9**:431. doi:10.1186/1471-2458-9-431

41 Green LA, Fryer GE, Yawn BP, et al. The ecology of medical care revisited. N Engl J Med 2001;**344**:2021–5. doi:10.1056/NEJM200106283442611

42 Institut National de Veille Sanitaire (InVS). Evolution des taux de participation au programme national de dépistage organisé du cancer du sein par classe d'âge, depuis 2005. http://www.invs.sante.fr/fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Cancers/Evaluation-des-programmes-de-depistage-des-cancers/Evaluation-du-programme-de-depistage-du-cancer-du-sein/Indicateurs-d-evaluation/Evolution-des-taux-de-participation-au-programme-national-de-depistage-organise-du-cancer-du-sein-par-classe-d-age-depuis-2005 (accessed 22 Sep2014).

43 Leuraud K, Jezewski-Serra D, Viguier J, et al. Colorectal cancer screening by guaiac faecal occult blood test in France: Evaluation of the programme two years after launching. Cancer Epidemiol 2013;**37**:959–67. doi:10.1016/j.canep.2013.07.008

44 Duport N. Données épidémiologiques sur le cancer du col de l'utérus - Etat des connaissances - Actualisation 2008. Institut de Veille Sanitaire 2008. http://opac.invs.sante.fr/doc_num.php?explnum_id=3243

45 Koh HK, Norton LA, Geller AC, et al. Evaluation of the American Academy of Dermatology's National Skin Cancer Early Detection and Screening Program. J Am Acad Dermatol 1996;**34**:971–8.

46 Carli P, De Giorgi V, Giannotti B, et al. Skin cancer day in Italy: method of referral to open access clinics and tumor prevalence in the examined population. Eur J Dermatol EJD 2003;**13**:76–9.

47 Stratigos A, Nikolaou V, Kedicoglou S, et al. Melanoma/skin cancer screening in a Mediterranean country: results of the Euromelanoma Screening Day Campaign in Greece. J Eur Acad Dermatol Venereol JEADV 2007;**21**:56–62. doi:10.1111/j.1468-3083.2006.01865.x

48 Mc Gee R, Elwood M, Williams S, et al. Who comes to skin checks? N Z Med J 1994;**107**:58–60.

49 Koh HK, Geller AC, Miller DR, et al. Who is being screened for melanoma/skin cancer? Characteristics of persons screened in Massachusetts. J Am Acad Dermatol 1991;**24**:271–7.

50 Paoli J, Danielsson M, Wennberg AM. Results of the 'Euromelanoma Day' screening campaign in Sweden 2008. J Eur Acad Dermatol Venereol JEADV 2009;**23**:1304–10. doi:10.1111/j.1468-3083.2009.03316.x

51 Rat C, Quereux G, Riviere C, et al. Targeted melanoma prevention intervention: a cluster randomized controlled trial. Ann Fam Med 2014;**12**:21–8. doi:10.1370/afm.1600

52 Veronesi A, Pizzichetta MA, De Giacomi C, et al. A two-year regional program for the early detection of cutaneous melanoma. Tumori 2003;**89**:1–5.

53 Aitken JF, Janda M, Elwood M, et al. Clinical outcomes from skin screening clinics within a community-based melanoma screening program. J Am Acad Dermatol 2006;**54**:105–14. doi:10.1016/j.jaad.2005.08.072

54 Engelberg D, Gallagher RP, Rivers JK. Follow-up and evaluation of skin cancer screening in British Columbia. J Am Acad Dermatol 1999;**41**:37–42.

55 Waldmann A, Nolte S, Geller AC, et al. Frequency of excisions and yields of malignant skin tumors in a population-based screening intervention of 360,288 whole-body examinations. Arch Dermatol 2012;**148**:903–10. doi:10.1001/archdermatol.2012.893

56 Bourgueil Y, Jusot Florence, Leleu Henri. Comment les soins primaires peuvent-ils contribuer à réduire les inégalités de santé ? Institut De Recherche et Documentation en Economie de le Santé 2012. http://www.irdes.fr/Publications/2012/Qes179.pdf

57 Macinko J, Starfield B, Shi L. The contribution of primary care systems to health outcomes within Organization for Economic Cooperation and Development (OECD) countries, 1970-1998. Health Serv Res 2003;**38**:831–65.

LEGENDS

Figure 1. Questionnaire used for the Self-Assessment of Melanoma Risk Score.

Figure 2. Healthcare journey 6 months after a postal proposal for an annual GP skin examination.

Figure 3. Participation in skin examinations by GPs and dermatologists among patients at elevated risk for melanoma based on a two-year follow-up.

TABLES

Table 1. Dermatologists' clinical and pathological conclusions according to the healthcare journey leading to consultation with a dermatologist.

		The patient consulted the dermatologist …			
	Total	**… as part of a dermatologist's follow-up**	**… after a GP referral**	**… on his/her own initiative**	**p[a]**
	N=616 n ; **%**	N=202 n ; **%**	N=254 n ; **%**	N=95 n ; **%**	
Clinical conclusion of the dermatologist					
• **Benign lesion**	248 ; ***40***	72 ; ***36***	110 ; ***43***	44 ; ***46***	0.13
• **Suspicious lesion**	368 ; ***60***	130 ; ***64***	144 ; ***57***	51 ; ***54***	0.13
- requiring a specialist follow-up	283 ; ***46***	109 ; ***54***	107 ; ***42***	35 ; ***37***	0.008
- requiring an excision	85 ; ***14***	21 ; ***10***	37 ; ***15***	16 ; ***17***	0.24
Pathological conclusions					
Cancerous lesions	26 ; ***4.2***	4 ; ***1.9***	14 ; ***5.5***	5 ; ***5.2***	0.12
- Melanoma	6	0	5	1	0.13
- Spinocellular carcinoma	5	0	2	1	0.40
- Basocellular carcinoma	15	4	7	3	0.82

[a] **Fisher or Chi-square test**

Table 2. Characteristics of melanomas diagnosed during the 2-year follow-up of the COPARIME cohort.

	N°	Gender	Patient age at diagnosis	Healthcare pathway	Type	Localisation	Breslow index (mm)	Delay between GP consultation and excision (days)
1st year of COPARIME targeted screening	1	F	31	Compliant	SSM	Forearm	0.16	24
	2	F	73	Compliant	Dubreuilh	Face	0	49
	3	M	64	Compliant	SSM	Back	0.8	49
	4	M	40	Compliant	SSM	Forearm	0.49	54
	5	M	51	Compliant	SSM	Back	0.245	106
	6	M	75	Compliant	Dubreuilh	Forearm	0.18	108
	7	F	34	Compliant	SSM	Thigh	0.52	124
	8				SSM	Thigh	0.15	124
	9	F	55	Patient's own initiative	SSM	Forearm	0	154
	10	M	56	Patient's own initiative	SSM	Back	0	286
2nd year of COPARIME targeted screening	11	F	71	Compliant	SSM	Thigh	0.45	33
	12	M	66	Compliant	Dubreuilh	Face	0	137
	13	M	59	Compliant	SSM	Bottom	0.38	191
	14	F	68	Referred in 2011, consulted after 2012 reminder	SSM	Calf	1.11	512
	15	M	42	Patient's own initiative	SSM	Back	0.43	513
	16	F	32	Referred in 2011, consulted after 2012 reminder	SSM	Back	0.242	709

	Breslow index (mm)			Delay between GP consultation and excision (days)		
	1st year	2nd year	p	1st year	2nd year	p
Mean	0.25	0.43	0.33[a]	107.8	349	0.077[a]
Median	0.17	0.405	0.65[b]	107	351	0.15[b]

F: Female, M: Male

SSM: Superficial spreading melanoma

[a] Student's t test

[b] Fisher test

Table 3: Patient participation and efficacy of a pilot melanoma targeted screening, after an annual reminder mailing

Table 3a. Description compared to the first year of the screening

	Year after annual reminder mailing		Year of inclusion		p
	%	*(n/N)*	%	*(n/N)*	
Proportion of included patients who attended the GP consultation	54.0	*(2021/3745)*	100.0	*(3917/3917)*	<0.001
Proportion of patients referred to a dermatologist	12.2	*(247/2021)*	38.3	*(1502/3917)*	<0.001
Proportion of referred patients who actually consulted the dermatologist	68.8	*(170/247)*	59.1	*(887/1502)*	0.003
Proportion of patients lost to follow-up	17.1	*(665/3897)*	2.6	*(102/3917)*	<0.001
Proportion of overall patients who had a dermatological skin examination	15.8	*(616/3897)*	23.9	*(938/3917)*	<0.001
Proportion of exeresis decision among dermatologist consultation	13.5	*(83/616)*	12.9	*(121/938)*	0.80
Proportion of malignant lesions among excised lesions	31.3	*(26/83)*	24.0	*(29/121)*	0.32
Crude incidence of melanoma	$160/10^5$	*(6/3745)*	$229/10^5$	*(9/3917)*	0.67

Table 3b. Subgroup analysis focusing on two populations at elevated risk of advanced melanoma

	Men older than 50	Others	p	>60 years old	<60 years old	p
	% *(n/N)*	% *(n/N)*		% *(n/N)*	% *(n/N)*	
Proportion of included patients who attended the GP consultation	66.0 *(281/426)*	52.4 *(1740/3319)*	<0.001	72.4 (516/713)	49.6 (1505/3032)	<0.001
Proportion of patients referred to a dermatologist	11.4 *(32/281)*	12.4 *(215/1740)*	0.72	10.7 (55/516)	12.8 (192/1505)	0.24
Proportion of referred patients who actually consulted the dermatologist	87.5 *(27/32)*	66.5 *(143/215)*	0.067	70.9 (39/55)	68.2 (131/192)	0.83
Proportion of patients lost to follow-up	10.0 *(43/430)*	18.0 *(522/2900)*	<0.001	8.0 (62/775)	19.0 (603/3174)	<0.001
Proportion of overall patients who had a dermatological skin examination	19.0 *(81/426)*	16.1 *(535/3319)*	0.15	17.7 (126/713)	16.2 (490/3032)	0.36
Proportion of exeresis decision among dermatologist consultation	21.0 *(17/81)*	11.6 *(62/535)*	0.029	15.9 (20/126)	12.0 (59/490)	0.32
Proportion of malignant lesions among excised lesions	66.7 *(12/18)*	21.5 *(14/65)*	<0.001	66.7 (14/21)	19.4 (12/62)	<0.001
Crude incidence of melanoma	$469/10^5$	$120/10^5$	0.14	$420/10^5$	$99/10^5$	0.09

Answer each question by checking the corresponding square:

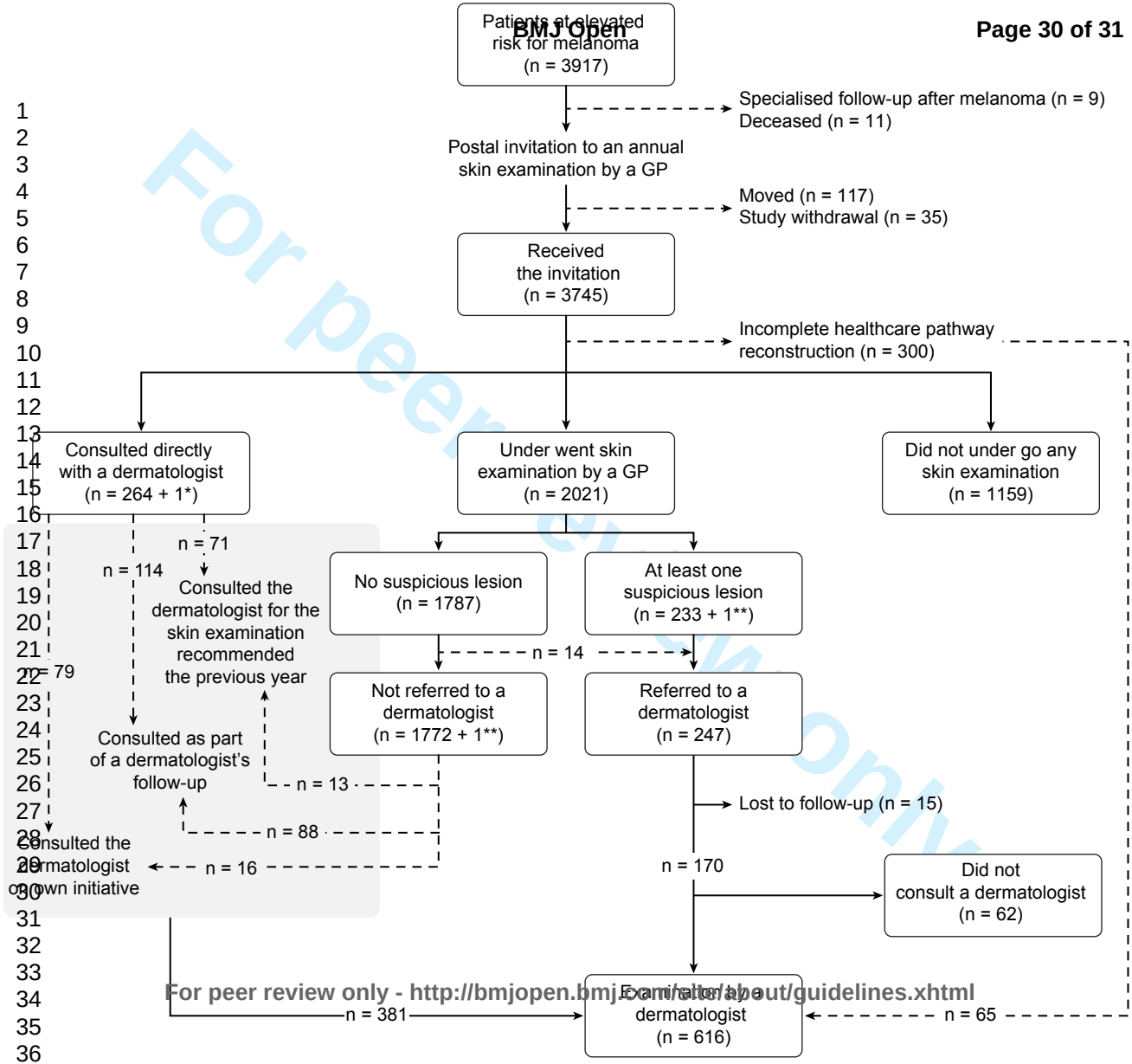
1. What type of skin do you have?
   . Skin type I: very fair skin, blond or red hair, light eyes (blue or green), never tan and always sunburn after sun exposure
   . Skin type II: fair skin, blond or light-brown hair, light eyes (blue or green), usually sunburn
   . Skin type III: deep skin, brown hair, light to medium eye colour
   . Skin type IV: olive skin, dark-brown hair, brown eyes
   . Skin type V: brown skin, black hair, black eyes
   . Skin type VI: black skin, black hair, black eyes
2. Do you have freckles? Yes / No
3. Approximately how many moles do you have on both arms? More than 20 / Fewer than 20
4. Have you had one or more episodes of a severe blistering sunburn during your childhood or teenage years? Yes / No
5. Have you lived in a country where sunshine is high (Africa, French West Indies, the southern United States, Australia…) for more than one year? Yes / No
6. Have you been diagnosed with melanoma (a skin cancer arising in melanocytes, the skin cells that make skin pigment) in the past? Yes / No
7. Have any of your first-degree relatives (parents, children, brother or sister) ever had melanoma? Yes / No / Don't know

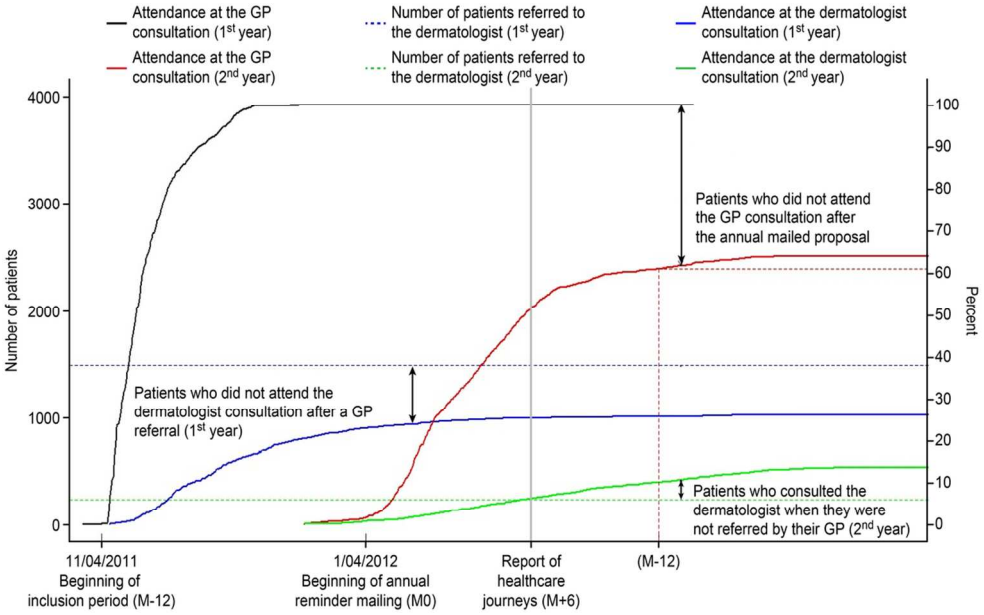
According to the SAMScore, a patient is considered at elevated risk for melanoma if at least one of these 3 criteria is met:

. First criterion: Presence of at least 3 risk factors among the following 7 risk factors: phototype I or II, a freckling tendency, a number of melanocytic nevi >20 on both arms, severe sunburn during childhood or teenage years, life in a country at low latitude, a history of previous melanoma, and a history of melanoma in a first-degree relative.

. Second criterion: Under 60 years of age and a number of melanocytic nevi >20 on both arms.

. Third criterion: Sixty years old or older and a freckling tendency.





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Proposal for an annual skin examination by a general practitioner for patients at high risk for melanoma: A French cohort study.

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ABSTRACT

Objective: To evaluate the efficacy of a targeted screening for melanoma in high-risk patients following the receipt of a mailed invitation to an annual skin examination by a general practitioner (GP).

Methods: A prospective cohort study was conducted in a primary care setting in western France. A total of 3,897 patients at elevated risk of melanoma (identified using the Self-Assessment of Melanoma Risk Score) consented to participate in a targeted melanoma screening project in 2011. One year later, the participants were invited by mail to consult their GP for an annual skin examination. Efficacy of the procedure was evaluated according to patient participation and the number of melanomas detected. The consultation dates and results were collected during the 12 months post-reminder and were analysed using SAS. Analyses of whether participation decreased compared with that during the year of inclusion and whether populations at risk for thick melanoma showed reduced participation in the screening were performed.

Results: Of the 3,745 patients who received the mailed invitation, 61.0% underwent a skin examination. The participation of patients at risk for thick melanoma (any patient over 60 years of age and men over 50 years of age) was significantly greater than that of the patients in the other subgroups (72.4% vs. 49.6%, $p<0.001$; and 66.0% vs. 52.4%, $p<0.001$, respectively). The patients referred to the dermatologist after one year were more compliant compared with those referred during the first year (68.8% vs. 59.1%, $p=0.003$). Six melanomas were detected within one year post-reminder; therefore, the incidence of melanoma in the study population was 160/100,000.

Conclusion: This study confirms the benefits of developing a targeted screening strategy in primary care. In particular, after the annual reminder, patient participation and the diagnosis of melanoma remained high in the patients at elevated risk of thick melanomas.

Keywords: melanoma; screening; early detection of cancer; primary healthcare

Registration number: NCT01610531

ARTICLE SUMMARY

Strengths and limitations of this study

- The study was conducted in a primary care setting.
- The participants were patients at elevated risk of melanoma who were recruited using a validated and reproducible procedure based on the Self-Assessment of Melanoma Risk Score.
- Six months after receiving an annual reminder to consult their general practitioner for a targeted screening for melanoma, 61.0% of the patients underwent a skin examination.
- The participation of patients at risk for thick melanoma was significantly above average.
- Six melanomas were detected. These results yielded a crude melanoma incidence of 160/100,000 in the cohort population and 469/100,000 in the men older than 50.

INTRODUCTION

In France, the incidence of melanoma is estimated at 10.8/100,000 for men and 11.0/100,000 for women [1]. Overall, the incidence increased by 3.5 between 1980 and 2012 [1]. Because the lesions are visible, they should be detected at an early stage through skin examination. However, in 2012, melanoma was responsible for 1,672 deaths in France [1]. The main prognostic factor is the Breslow thickness (in millimetres) at the time of diagnosis [2]. The 5-year survival rate of patients with localised melanoma is 98.1%, compared with only 16.1% for metastatic melanoma patients [3]. Despite these findings, routine screening by full skin examination is not recommended in France [4], the United States [5], Australia or New Zealand, although the latter has the highest incidence of this disease worldwide [6,7]. Indeed, the efficacy of routine screening in decreasing the mortality rate for these patients has not been proven [5], and routine screening would be expensive to perform [8].

Conducting targeted screenings based on the identification of high-risk subjects could be a more valuable [9] and cost-effective strategy [8,10,11]. The following main risk factors for melanoma are well known [12–14]: a personal or family history of melanoma, the presence of greater than 40 nevi, the presence of atypical nevi, skin phenotype I or II, freckles and actinic damage, and a history of sunburns. Certain demographic groups have also been identified as being at higher risk of *thick* melanoma [9,15], including men, individuals over 60 years of age [16,17], and men over 50 years of age [18]. However, there is a need to define the best way to identify, screen, and follow individuals at high-risk of primary cutaneous melanoma [19].

A low physician density has also been associated with the identification of thick melanomas [20–22]. Melanomas tend to be thinner when they are detected by physicians rather than patients and also when they are detected during screening skin examination

rather than during routine care [17,23–27]. However, only 20% of patients who have had melanoma report that they previously consulted a dermatologist [28]. Therefore, general practitioners (GPs) could play a significant role in the screening of these patients. One study has reported that the proportion of melanomas diagnosed by GPs in France increased from 24% in 2004 to 42% in 2008 following the implementation of a system requiring patients to register their attending physician [29].

Based on these findings, our team has developed a targeted melanoma screening procedure grounded in primary care, using the Self-Assessment of Melanoma Risk Score (SAMScore). This score is based on a 7-item self-administered questionnaire (Figure 1) that a patient can answer without specific medical knowledge (30-32) and allows for the selection of a population at high risk of melanoma during primary care consultations [30–33]. The SAMScore algorithm allows for the expression of risk in a dichotomous format (either at elevated risk or not for melanoma) (Figure 1). According to the SAMScore, a patient is considered at elevated risk for melanoma if at least one of the following 3 criteria is met: 1) the presence of at least 3 risk factors among the following 7 risk factors: phenotype I or II, a freckling tendency, >20 melanocytic nevi on both arms, experienced severe sunburn during the childhood or teenage years, resides in a country at low latitude, a history of previous melanoma, and a history of melanoma in a first-degree relative; 2) under 60 years of age and >20 melanocytic nevi on both arms; and 3) sixty years of age or older with a freckling tendency. Previous research based on a literature review has suggested a relative risk of 13.77 in the selected high-risk population [31-32]. The SAMScore has been used to create a cohort of patients at high risk of melanoma (COPARIME) who were then asked to participate in a pilot targeted screening for melanoma (NCT01610531) [33]. The targeted melanoma screening procedure comprised the following 3 steps: 1) identifying high-risk patients using the SAMScore; 2) asking GPs to perform a total skin examination on these high-risk patients; and 3) referring patients to

a dermatologist if needed (for patients requiring a specialist opinion according to the GP). Between April and October 2011, 3,917 patients were included, nine of whom had melanoma. The crude incidence observed during the first year of screening (229/100,000) highlighted the potential benefit of such a targeted screening [33].

However, the generalizability of the findings based on a one-year intervention might be low. A major issue is the compliance of high-risk patients selected by the SAMScore who would be asked to consult yearly for melanoma screening and to consult a dermatologist in the case of a suspicious lesion [34]. Specific attention should be paid to patients at high risk of *thick* melanoma (including men, individuals over 60 years of age and men over 50 years of age) because their concern for melanoma screening has been reported to be lower compared with other high-risk patients [16-18].

Our team contacted all patients at risk of melanoma from the COPARIME cohort at one year after their inclusion in the targeted screening procedure. They received a mailed invitation to reconsult their GP for an annual skin examination. The aim of the study was to evaluate the efficacy of the mailed reminder, based on the following two variables: patient participation (with a specific focus on populations at risk of thick melanoma) and the number of melanomas detected.

METHODS

Design of the study

This study was based on a prospective follow-up of the COPARIME cohort. The patients were initially enrolled between April 11 and October 30, 2011, by 78 GP volunteers in western France, specifically in the departments of Loire-Atlantique and Vendée. All dermatologists in both departments participated in the study. The dermatologist density is 5.3/100,000 inhabitants in Loire-Atlantique, a predominantly urban department, and 2.1/100,000 inhabitants in Vendée, a more rural department. These physician densities are comparable to those of other French departments (national mean: 5.3/100,000) [35].

Participants

The eligibility criteria to receive the reminder at one year were as follows: being at high risk for melanoma according to the SAMScore, having agreed to participate in the targeted melanoma screening one year earlier, being over 18, and having no personal history of melanoma. Twenty patients were excluded from the COPARIME database, including 9 who had developed melanoma during the year since initially participating and had been directly recommended for a dermatologist follow-up and 11 who had died. As a result, a total of 3,897 patients were eligible (Figure 2).

Annual skin examination by general practitioner

An invitation to reconsult their GP for an annual skin examination was sent to eligible patients by mail at one year after their inclusion in the cohort.

The GP was asked to perform a total skin examination. Patients were referred to a dermatologist based on the opinion of the GP (as in routine care). The dermatologists were asked to classify their examinations of these referred patients according to the following three categories: “benign lesion”, “lesion to monitor” and “indication for exeresis”. When exeresis was indicated, the last step was anatomopathological examination.

Data collection

In addition to sending a reminder to the patients, each GP was mailed a table summarising the following data to be collected for each patient: the date of skin examination, the identification or not of a suspicious lesion, and whether the patient was referred to a dermatologist. An updated table was sent to the GPs at months 6 and 12. If data were missing at one year after sending the reminder, an investigator contacted the GP by telephone and offered to visit the medical practice to facilitate data collection.

One year after the reminder was mailed to the last patient in the cohort, each dermatologist was mailed a table summarising the data to be collected for each patient, including the date of the dermatological consultation and the conclusion derived from the skin examination, i.e., “benign lesion”, “lesion to monitor”, or “indication for exeresis”. The anatomopathological result was also recorded when available. If data were missing, an investigator contacted the dermatologist by telephone and offered to visit the medical practice.

Between June and December 2013, all patients for whom no data were available were recontacted to determine whether they had consulted a dermatologist. All of the data collected during these telephone calls with patients were then confirmed or invalidated based on data from a physician (GP or dermatologist).

All of the data were recorded in an Access database.

Efficacy: patient participation and number of melanomas detected

Participation in the follow-up annual skin examination by the GP was assessed at 6 months after mailing the invitation.

Patient participation following the mailing of the invitation was analysed after the classification of the patients into the following 6 categories: 1) underwent the skin examination by the GP as expected; 2) directly consulted a dermatologist without reconsulting the GP, even though he/she had not consulted a dermatologist when his/her GP had referred him/her the previous year; 3) directly reconsulted his/her dermatologist as part of his/her dermatological follow-up; 4) directly reconsulted his/her dermatologist on his/her own initiative; 5) had no skin examination by his/her GP and no dermatological consultation; and 6) was referred to a dermatologist following examination by his/her GP but did not consult the dermatologist.

Melanoma cases were described using pathological reports.

Statistical analysis

Quantitative data are presented as the mean and median. Subgroup analysis was performed for the men, patients over 60 years of age, men over 50 years of age, and patients living in rural areas. Data from the first year were compared with data from the second year using the Chi-square and Fisher's exact tests. The GP effect was tested using a Fisher variance ratio test. Statistical significance was set at 0.05. R 3.10.0 software was used.

Opinion of the ethics committee

The ethics committee of Tours University Hospital has given its favourable opinion on the performance of the study (n°2011-R2-BRD 10/11-N).

RESULTS

Patient demographics

Of the 3,897 patients, 117 moved without leaving a forwarding address, and 35 discontinued their participation in the study, leaving 3,745 patients for integration into analysis. The mean age of the patients was 44.5 (±15.6) years, and there were 1,197 (32%) men. In total, 713 (19%) patients were over 60 years of age, and 426 (11.3%) were men over 50 years of age. Finally, 2,427 (64.8%) patients lived in Loire-Atlantique, 1,206 (32.2%) in Vendée, and 112 (3.25%) in other departments.

Patient participation

After the one-year follow-up, 61% of the patients included in the targeted screening procedure reconsulted their GP, and 16% reconsulted a dermatologist (Figure 3). A total of 17.1% of the cohort patients were lost to follow-up.

Figure 2 shows the 6 methods of patient participation, analysed at 6 months after the invitation was mailed to reconsult. A total of 264 (7%) patients directly consulted a dermatologist, 2,021 (54%) reconsulted their GP, and 1,159 (31%) had no skin monitoring.

The proportion of referred patients who actually consulted a dermatologist increased after the reminder at one year compared with that upon initial inclusion in the screening (68.8% vs. 59.1%, $p<0.001$). The GP effect, tested as a random factor, was not significant ($p=0.32$). However, the overall proportion of cohort patients who consulted a dermatologist was lower (15.8% vs. 23.9%, $p<0.001$) because the proportion of patients referred to a dermatologist by the GPs was lower (12.2% vs. 38.3%, $p<0.001$) (Table 1). The GP effect, tested as a random factor, was not significant ($p=0.10$).

Melanoma cases

A total of 83 patients underwent exeresis, and 6 melanomas, 5 squamous cell carcinomas and 15 basal cell carcinomas were diagnosed. The characteristics of the 6 melanomas are provided in Table 2. Of the 6 melanomas, 5 were identified among the patients initially referred by their GP. The incidence of melanoma standardised to the populations of both departments was $183.7/10^5$ for men and $98.7/10^5$ for women.

The median thickness of the melanomas detected during the second year was 0.405 mm (Table 2). One melanoma was greater than 1 mm thick, which was identified in a patient who had not consulted a dermatologist after having been referred the first year.

In men over 50 years of age, the exeresis rate (21.0% vs. 11.6%, p=0.029) and the number of malignant lesions identified after exeresis (66.7% vs. 21.5%, p<0.001) were higher compared with the reference group (Table 3). In patients over 60 years of age, the number of malignant lesions identified after exeresis (66.7% vs. 19.4%, p<0.001) was higher compared with the reference group (Table 3).

DISCUSSION

Main results

Six months after receiving the annual reminder to schedule a total skin examination with their GP, 61.0% of the patients underwent a skin examination. Of them, 7.1% directly consulted a dermatologist. Of the patients who consulted their GP, 12.2% were referred to a specialist. The participation of populations at risk for thick melanoma was significantly above average. Six new melanomas were detected, corresponding to a crude incidence of 160/100,000.

Strengths and weaknesses

The strengths of this study are the size of the study population, the screening procedure initiated under primary care and under real care conditions, the use of a single validated and reproducible tool to detect high-risk subjects, and the prospective follow-up of the cohort.

This study also has certain limitations, including the number of patients lost to follow-up, the inclusion bias (women and young subjects were over-represented in the population) and the absence of data on the false negative rate of the procedure. Female over-representation is usually found in skin screening programs [36–39] and more generally in cancer screening [40,41]. This bias could also be related to the population seeking consultation in general practice, which is not entirely representative of the general population [33,42].

Last but not least, this study was conducted in a French setting and involved GPs who were volunteers; thus, the generalizability of the findings should be considered with caution. The study design was grounded in a healthcare system in which GPs have a

mission of regulating access to secondary care. This organisation has been implemented in a large majority of European countries [43]. However, national specificities may affect the referral and management procedures. Other variations may also appear in relation to discrepancies in the use of dermoscopy.

Interpretation of the results and comparison with data from the literature

The 61.0% rate of participation in the annual skin examination is higher than the rates observed for other cancers in France, including 52.1% for mammography [44], 34.3% for Hemoccult II [45] and 58.7% for cervical smear [46]. This good participation rate, observed after the one-year reminder, is a significant result that indicates the success of the screening. Offering a targeted screening rather than a screening of the general population could be associated with better participation.

Six melanomas with a median Breslow thickness of 0.405 mm were diagnosed during the second year of follow-up, and only one melanoma was greater than 1 mm thick. Similarly, other authors have reported that screening procedures help to identify predominantly thin lesions with a median Breslow thickness of approximately 0.3 mm [32,47,48]. The standardised incidence of melanoma in the high-risk population in this study was much higher than that which has been established in this geographic area (7.9 and 3.7 times higher for men and women, respectively). This increased incidence confirms that identifying patients at elevated risk of melanoma is relevant. This result is novel because most studies have only reported the benefit of a screening procedure immediately after the intervention. The observation of transient over-detection in these studies did not allow for an assessment of the benefit that would have been obtained if the screening procedure had been extended [32,33,49].

The present study confirms the potential benefit of GP consultation. First, 5 of the 6 new melanoma cases were identified among patients referred by their GP. Second, the concentration effect related to GP consultation was increased. Indeed, the proportion of patients referred to a dermatologist by their GP decreased during the second year compared with the first year (12.2% vs. 38.3%). This proportion is more consistent with previously published data that have revealed proportions of referred patients ranging from 7.4% to 26% [36,50–52]. This evolution could be explained by the need for GPs to perform an initial dermatologist reference examination during the year of inclusion, whereas their role would subsequently be to ensure the absence of evolution of pre-existing lesions.

The benefit of the proposed screening seemed the highest in the populations at risk of thick melanoma. Men, men over 50 years of age, and subjects over 60 years of age accounted for 32%, 11,3% and 19% of the cohort population, respectively, but they accounted for 50%, 33% and 50% of the melanoma patients, which is consistent with the findings of other authors [18,51,53]. No very thick melanomas (> 3 mm) were detected in our high-risk population over the course of two years. We were not able to conclude whether this result was due to the efficacy of the screening procedure or if it was simply related to the low incidence of thick melanomas in the population. The only melanoma greater than 1 mm was paradoxically detected during the second year: the corresponding patient had been referred to a dermatologist during the first year, but he did not consult the dermatologist until more than one year later. For this type of minimally compliant patient, our mailed reminder could have communicated to the patient that he or she was responsible for any appointment made. Thus, the benefits of a primary care-based targeted screening on the incidence of very thick melanomas could be due to not only the involvement of GPs

trained in screening [52] but also the impact of a simple annual reminder on minimally compliant patients.

Finally, 95 patients consulted a dermatologist on their own initiative, one of whom had a melanoma. This finding is consistent with the results of other studies showing that certain subjects participating in skin screening programs appropriately pursue consultations on their own [36,49,54-57]. In our study, it is likely that patients who were sensitised to their risk status and educated in skin self-examination by their GP directly consulted a dermatologist when they identified a suspicious lesion.

Practical implications and perspectives

In our study, we evaluated a generic procedure that addresses the reported limits of numerous national guidelines [19]. The identification of high-risk individuals was based on a validated tool. We assessed a reproducible procedure for the clinical management of individuals defined as high risk, involving the mailing of a yearly invitation for a clinical skin examination performed by a GP.

More than half of the patients identified as being at risk for melanoma according to the SAMScore responded positively to our mailed reminder about scheduling an annual skin examination with their GP. The high melanoma incidence and low melanoma thickness identified in this study both confirm the value of a targeted screening conducted in primary care.

Extending the follow-up of our cohort would allow for an assessment of the proportion of false negatives related to GPs' examinations. Other major issues that should be addressed include assessments of the follow-up pace to be proposed in this population and the related

costs. The validation of a beneficial effect of this screening procedure on mortality will require a randomised study.

Ethical approval

The ethics committee of the University Hospital of Tours approved this study (n° 2011-R2-BRD 10/11-N).

STATEMENTS

a. CONTRIBUTORSHIP STATEMENT

CR conceived of the study, participated in its design and supervision, and was responsible for the GP network and for drafting the manuscript. CG participated in the design of the study, was responsible for the data collection, and helped to draft the manuscript. GQ participated in the design of the study, managed the pathological reports, and helped to draft the manuscript. MD participated in the data collection and helped to draft the manuscript. AG performed statistical analysis and helped to draft the manuscript. AK and BD participated in the design, were responsible for the dermatologist network, and provided administrative and technical support. JMN participated in the design of the study, was responsible for statistical analysis and study supervision and helped to draft the manuscript. All authors read and approved the final manuscript.

b. COMPETING INTERESTS

None reported. The sponsor (French National Institute of Cancer) had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

c. FUNDING

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d. DATA SHARING STATEMENT

No additional data available

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REFERENCES

1 Binder-Foucard F, Belot A, Delafosse P, et al. Estimation nationale de l'incidence et de la mortalité par cancer en France entre 1980 et 2012. Partie 1 - Tumeurs solides. Saint-Maurice (Fra): Institut de Veille Sanitaire 2013.

2 Balch CM, Gershenwald JE, Soong S-J, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol Off J Am Soc Clin Oncol 2009;**27**:6199–206. doi:10.1200/JCO.2009.23.4799

3 How Many People Survive 5 Years Or More after Being Diagnosed with Melanoma of the Skin? http://seer.cancer.gov/statfacts/html/melan.html#survival (accessed 10 Sep2014).

4 Haute Autorité de Santé. Stratégie de diagnostic précoce du mélanome. 2006.www.has-sante.fr/

5 U.S. Preventive Services Task Force. Screening for skin cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009;**150**:188–93.

6 Cancer Council Australia, New Zealand, Ministry of Health, et al. Clinical practice guidelines for the management of melanoma in Australia and New Zealand: evidence-based best practice guidelines. Sydney, N.S.W.; New Zealand: : Cancer Council Australia : Australia Cancer Network ; Ministry of Health 2008.

7 Bray F, Ren J-S, Masuyer E, et al. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 2013;**132**:1133–45. doi:10.1002/ijc.27711

8 Losina E, Walensky RP, Geller A, et al. Visual screening for malignant melanoma: a cost-effectiveness analysis. Arch Dermatol 2007;**143**:21–8. doi:10.1001/archderm.143.1.21

9 Curiel-Lewandrowski C, Chen SC, Swetter SM, et al. Screening and prevention measures for melanoma: is there a survival advantage? Curr Oncol Rep 2012;**14**:458–67. doi:10.1007/s11912-012-0256-6

10 Freedberg KA, Geller AC, Miller DR, et al. Screening for malignant melanoma: A cost-effectiveness analysis. J Am Acad Dermatol 1999;**41**:738–45.

11 Gordon LG, Rowell D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP Published Online First: 2 August 2014. doi:10.1097/CEJ.0000000000000056

12 Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur J Cancer Oxf Engl 1990 2005;**41**:28–44. doi:10.1016/j.ejca.2004.10.015

13 Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer Oxf Engl 1990 2005;**41**:45–60. doi:10.1016/j.ejca.2004.10.016

14 Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur J Cancer Oxf Engl 1990 2005;**41**:2040–59. doi:10.1016/j.ejca.2005.03.034

15 Geller AC, Swetter SM, Oliveria S, et al. Reducing mortality in individuals at high risk for advanced melanoma through education and screening. J Am Acad Dermatol 2011;**65**:S87–94. doi:10.1016/j.jaad.2011.05.045

16 Geller AC, Elwood M, Swetter SM, et al. Factors related to the presentation of thin and thick nodular melanoma from a population-based cancer registry in Queensland Australia. Cancer 2009;**115**:1318–27. doi:10.1002/cncr.24162

17 Swetter SM, Pollitt RA, Johnson TM, et al. Behavioral determinants of successful early melanoma detection: role of self and physician skin examination. Cancer 2012;**118**:3725–34. doi:10.1002/cncr.26707

18 Geller AC, Sober AJ, Zhang Z, et al. Strategies for improving melanoma education and screening for men age >or= 50 years: findings from the American Academy of Dermatological National Skin Cancer Sreening Program. Cancer 2002;**95**:1554–61. doi:10.1002/cncr.10855

19 Watts CG, Dieng M, Morton RL, Mann GJ, Menzies SW, Cust AE. Clinical practice guidelines for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma: a systematic review. Br J Dermatol. 2015;**172**:33-47.

20 Van Durme DJ, Ullman R, Campbell RJ, et al. Effects of physician supply on melanoma incidence and mortality in Florida. South Med J 2003;**96**:656–60. doi:10.1097/01.SMJ.0000053569.81565.19

21 Stitzenberg KB, Thomas NE, Dalton K, et al. Distance to diagnosing provider as a measure of access for patients with melanoma. Arch Dermatol 2007;**143**:991–8. doi:10.1001/archderm.143.8.991

22 Aneja S, Aneja S, Bordeaux JS. Association of increased dermatologist density with lower melanoma mortality. Arch Dermatol 2012;**148**:174–8. doi:10.1001/archdermatol.2011.345

23 Helfand M, Mahon SM, Eden KB, et al. Screening for skin cancer. Am J Prev Med 2001;**20**:47–58. doi:10.1016/S0749-3797(01)00258-6

24 Epstein DS, Lange JR, Gruber SB, et al. Is physician detection associated with thinner melanomas? JAMA J Am Med Assoc 1999;**281**:640–3.

25 McPherson M, Elwood M, English DR, et al. Presentation and detection of invasive melanoma in a high-risk population. J Am Acad Dermatol 2006;**54**:783–92. doi:10.1016/j.jaad.2005.08.065

26 Aitken JF, Elwood M, Baade PD, et al. Clinical whole-body skin examination reduces the incidence of thick melanomas. Int J Cancer J Int Cancer 2010;**126**:450–8. doi:10.1002/ijc.24747

27 Richard MA, Grob JJ, Avril MF, et al. Delays in diagnosis and melanoma prognosis (II): the role of doctors. Int J Cancer J Int Cancer 2000;**89**:280–5.

28 Geller AC, Koh HK, Miller DR, et al. Use of health services before the diagnosis of melanoma: implications for early detection and screening. J Gen Intern Med 1992;**7**:154–7.

29 Grange F, Barbe C, Mas L, et al. The role of general practitioners in diagnosis of cutaneous melanoma: a population-based study in France. Br J Dermatol 2012;**167**:1351–9. doi:10.1111/j.1365-2133.2012.11178.x

30 Quéreux G, Nguyen J-M, Volteau C, et al. Creation and test of a questionnaire for self-assessment of melanoma risk factors: Eur J Cancer Prev 2010;**19**:48–54. doi:10.1097/CEJ.0b013e328333d113

31 Quéreux G, Moyse D, Lequeux Y, et al. Development of an individual score for melanoma risk: Eur J Cancer Prev 2011;**20**:217–24. doi:10.1097/CEJ.0b013e32834474ae

32 Quéreux G, Nguyen J-M, Cary M, et al. Validation of the Self-Assessment of Melanoma Risk Score for a melanoma-targeted screening. Eur J Cancer Prev 2012;**21**:588–95. doi:10.1097/CEJ.0b013e328353ed68

33 Rat C, Quereux G, Grimault C, et al. Melanoma incidence and patient compliance in a targeted melanoma screening intervention. One-year follow-up in a large French cohort of high-risk patients. Eur J Gen Pract 2014:1–7. doi:10.3109/13814788.2014.949669

34 Rat C, Quereux G, Monegier du Sorbier M, et al. Patients at elevated risk of melanoma: individual predictors of non-compliance to GP referral for a dermatologist consultation. Prev Med 2014;**64**:48–53. doi:10.1016/j.ypmed.2014.03.029

35 Démographie médicale interactive | Démographie médicale. Cons. Natl. Médecins. http://demographie.medecin.fr/demographie (accessed 13 Sep2014).

36 Breitbart EW, Waldmann A, Nolte S, et al. Systematic skin cancer screening in Northern Germany. J Am Acad Dermatol 2012;**66**:201–11. doi:10.1016/j.jaad.2010.11.016

37 Andrulonis R, Secrest AM, McGuire ST, et al. The influence of age and sex on reasons for seeking and expected benefits of skin cancer screening. Arch Dermatol 2010;**146**:1097–102. doi:10.1001/archdermatol.2010.254

38 De Rooij MJ, Rampen FH, Schouten LJ, et al. Factors influencing participation among melanoma screening attenders. Acta Derm Venereol 1997;**77**:467–70.

39 Argenziano G, Zalaudek I, Hofmann-Wellenhof R, et al. Total body skin examination for skin cancer screening in patients with focused symptoms. J Am Acad Dermatol 2012;**66**:212–9. doi:10.1016/j.jaad.2010.12.039

40 Davis JL, Buchanan KL, Katz RV, et al. Gender differences in cancer screening beliefs, behaviors, and willingness to participate: implications for health promotion. Am J Mens Health 2012;**6**:211–7. doi:10.1177/1557988311425853

41 Sach TH, Whynes DK. Men and women: beliefs about cancer and about screening. BMC Public Health 2009;**9**:431. doi:10.1186/1471-2458-9-431

42 Green LA, Fryer GE, Yawn BP, et al. The ecology of medical care revisited. N Engl J Med 2001;**344**:2021–5. doi:10.1056/NEJM200106283442611

43 Masseria C, Irwin R, Thomson S, Gemmill M, Mossialos E. Primary care in Europe. European Commission report. 2009.

44 Institut National de Veille Sanitaire (InVS). Evolution des taux de participation au programme national de dépistage organisé du cancer du sein par classe d'âge, depuis 2005. http://www.invs.sante.fr/fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Cancers/Evaluation-des-programmes-de-depistage-des-cancers/Evaluation-du-programme-de-depistage-du-cancer-du-sein/Indicateurs-d-evaluation/Evolution-des-taux-de-participation-au-programme-national-de-depistage-organise-du-cancer-du-sein-par-classe-d-age-depuis-2005 (accessed 22 Sep2014).

45 Leuraud K, Jezewski-Serra D, Viguier J, et al. Colorectal cancer screening by guaiac faecal occult blood test in France: Evaluation of the programme two years after launching. Cancer Epidemiol 2013;**37**:959–67. doi:10.1016/j.canep.2013.07.008

46 Duport N. Données épidémiologiques sur le cancer du col de l'utérus - Etat des connaissances - Actualisation 2008. Institut de Veille Sanitaire 2008. http://opac.invs.sante.fr/doc_num.php?explnum_id=3243

47 Koh HK, Norton LA, Geller AC, et al. Evaluation of the American Academy of Dermatology's National Skin Cancer Early Detection and Screening Program. J Am Acad Dermatol 1996;**34**:971–8.

48 Carli P, De Giorgi V, Giannotti B, et al. Skin cancer day in Italy: method of referral to open access clinics and tumor prevalence in the examined population. Eur J Dermatol EJD 2003;**13**:76–9.

49 Stratigos A, Nikolaou V, Kedicoglou S, et al. Melanoma/skin cancer screening in a Mediterranean country: results of the Euromelanoma Screening Day Campaign in Greece. J Eur Acad Dermatol Venereol JEADV 2007;**21**:56–62. doi:10.1111/j.1468-3083.2006.01865.x

50 Veronesi A, Pizzichetta MA, De Giacomi C, et al. A two-year regional program for the early detection of cutaneous melanoma. Tumori 2003;**89**:1–5.

51 Aitken JF, Janda M, Elwood M, et al. Clinical outcomes from skin screening clinics within a community-based melanoma screening program. J Am Acad Dermatol 2006;**54**:105–14. doi:10.1016/j.jaad.2005.08.072

52 Engelberg D, Gallagher RP, Rivers JK. Follow-up and evaluation of skin cancer screening in British Columbia. J Am Acad Dermatol 1999;**41**:37–42.

53 Waldmann A, Nolte S, Geller AC, et al. Frequency of excisions and yields of malignant skin tumors in a population-based screening intervention of 360,288 whole-body examinations. Arch Dermatol 2012;**148**:903–10. doi:10.1001/archdermatol.2012.89348

54 Mc Gee R, Elwood M, Williams S, et al. Who comes to skin checks? N Z Med J 1994;**107**:58–60.

55 Koh HK, Geller AC, Miller DR, et al. Who is being screened for melanoma/skin cancer? Characteristics of persons screened in Massachusetts. J Am Acad Dermatol 1991;**24**:271–7.

56 Paoli J, Danielsson M, Wennberg AM. Results of the 'Euromelanoma Day' screening campaign in Sweden 2008. J Eur Acad Dermatol Venereol JEADV 2009;**23**:1304–10. doi:10.1111/j.1468-3083.2009.03316.x

57 Rat C, Quereux G, Riviere C, et al. Targeted melanoma prevention intervention: a cluster randomized controlled trial. Ann Fam Med 2014;**12**:21–8. doi:10.1370/afm.1600

LEGENDS

Figure 1. Questionnaire used for the Self-Assessment of Melanoma Risk Score.

Figure 2. Participation among patients at elevated risk of melanoma at 6 months after a mailed reminder for an annual GP skin examination.

Figure 3. Participation in skin examinations by GPs and dermatologists among patients at elevated risk of melanoma based on a two-year follow-up.

TABLES

Table 1. Patient participation in a pilot melanoma targeted screening after an annual mailed reminder.

	Year after annual reminder mailing		Year of inclusion		p
	%	*(n/N)*	%	*(n/N)*	
Proportion of included patients who attended the GP consultation	54.0	*(2021/3745)*	100.0	*(3917/3917)*	<0.001
Proportion of patients referred to a dermatologist	12.2	*(247/2021)*	38.3	*(1502/3917)*	<0.001
Proportion of referred patients who actually consulted the dermatologist	68.8	*(170/247)*	59.1	*(887/1502)*	0.003
Proportion of patients lost to follow-up	17.1	*(665/3897)*	2.6	*(102/3917)*	<0.001
Proportion of overall patients who had a dermatological skin examination	15.8	*(616/3897)*	23.9	*(938/3917)*	<0.001

Table 2. Characteristics of melanomas diagnosed during the 2-year follow-up of the COPARIME cohort.

	N°	Gender	Patient age at diagnosis	Healthcare pathway	Type	Localisation	Breslow index (mm)	Delay between GP consultation and excision (days)
1st year of COPARIME targeted screening	1	F	31	Compliant	SSM	Forearm	0.16	24
	2	F	73	Compliant	Dubreuilh	Face	0	49
	3	M	64	Compliant	SSM	Back	0.8	49
	4	M	40	Compliant	SSM	Forearm	0.49	54
	5	M	51	Compliant	SSM	Back	0.245	106
	6	M	75	Compliant	Dubreuilh	Forearm	0.18	108
	7	F	34	Compliant	SSM	Thigh	0.52	124
	8				SSM	Thigh	0.15	124
	9	F	55	Patient's own initiative	SSM	Forearm	0	154
	10	M	56	Patient's own initiative	SSM	Back	0	286
2nd year of COPARIME targeted screening	11	F	71	Compliant	SSM	Thigh	0.45	33
	12	M	66	Compliant	Dubreuilh	Face	0	137
	13	M	59	Compliant	SSM	Bottom	0.38	191
	14	F	68	Referred in 2011, consulted after 2012 reminder	SSM	Calf	1.11	512
	15	M	42	Patient's own initiative	SSM	Back	0.43	513
	16	F	32	Referred in 2011, consulted after 2012 reminder	SSM	Back	0.242	709

	Breslow index (mm)			Delay between GP consultation and excision (days)		
	1st year	2nd year	p	1st year	2nd year	p
Mean	0.25	0.43	0.33[a]	107.8	349	0.077[a]
Median	0.17	0.405	0.65[b]	107	351	0.15[b]

F: Female, M: Male

SSM: Superficial spreading melanoma

[a] Student's t test

[b] Fisher test

Table 3: Malignant lesions and participation in populations at elevated risk of advanced melanoma

	Men older than 50	Others	p	>60 years old	<60 years old	p
	% (n/N)	*% (n/N)*		*% (n/N)*	*% (n/N)*	
Proportion of included patients who attended the GP consultation	66.0 *(281/426)*	52.4 *(1740/3319)*	<0.001	72.4 (516/713)	49.6 (1505/3032)	<0.001
Proportion of patients referred to a dermatologist	11.4 *(32/281)*	12.4 *(215/1740)*	0.72	10.7 (55/516)	12.8 (192/1505)	0.24
Proportion of referred patients who actually consulted the dermatologist	87.5 *(27/32)*	66.5 *(143/215)*	0.067	70.9 (39/55)	68.2 (131/192)	0.83
Proportion of patients lost to follow-up	10.0 *(43/430)*	18.0 *(522/2900)*	<0.001	8.0 (62/775)	19.0 (603/3174)	<0.001
Proportion of overall patients who had a dermatological skin examination	19.0 *(81/426)*	16.1 *(535/3319)*	0.15	17.7 (126/713)	16.2 (490/3032)	0.36
Proportion of exeresis decision among dermatologist consultation	21.0 *(17/81)*	11.6 *(62/535)*	0.029	15.9 (20/126)	12.0 (59/490)	0.32
Proportion of malignant lesions among excised lesions	66.7 *(12/18)*	21.5 *(14/65)*	<0.001	66.7 (14/21)	19.4 (12/62)	<0.001
Crude incidence of melanoma	$469/10^5$	$120/10^5$	0.14	$420/10^5$	$99/10^5$	0.09

Answer each question by circling the corresponding option:

1. What phenotype of skin do you have?
   . Skin phenotype I: very fair skin, blond or red hair, light eyes (blue or green), never tan and always sunburn after sun exposure
   . Skin phenotype II: fair skin, blond or light-brown hair, light eyes (blue or green), usually sunburn
   . Skin phenotype III: deep skin, brown hair, light to medium eye colour
   . Skin phenotype IV: olive skin, dark-brown hair, brown eyes
   . Skin phenotype V: brown skin, black hair, black eyes
   . Skin phenotype VI: black skin, black hair, black eyes
2. Do you have freckles? Yes / No
3. Approximately how many moles do you have on both arms? More than 20 / Fewer than 20
4. Have you had one or more episodes of a severe blistering sunburn during your childhood or teenage years? Yes / No
5. Have you lived in a country where the level of sunshine is high (Africa, French West Indies, the southern United States, Australia, etc.) for more than one year? Yes / No
6. Have you been diagnosed with melanoma (a skin cancer arising in melanocytes, the skin cells that make skin pigment) in the past? Yes / No
7. Have any of your first-degree relatives (parents, children, brother or sister) ever had melanoma? Yes / No / Don't know

According to the SAMScore, a patient is considered at elevated risk for melanoma if at least one of the following 3 criteria is met:

. First criterion: The presence of at least 3 risk factors among the following 7 risk factors: skin phenotype I or II, a freckling tendency, >20 melanocytic nevi on both arms, experienced severe sunburn during their childhood or teenage years, residing in a country at low latitude, a history of previous melanoma, and a history of melanoma in a first-degree relative.

. Second criterion: Under 60 years of age and >20 melanocytic nevi on both arms.

. Third criterion: Sixty years of age or older and a freckling tendency.

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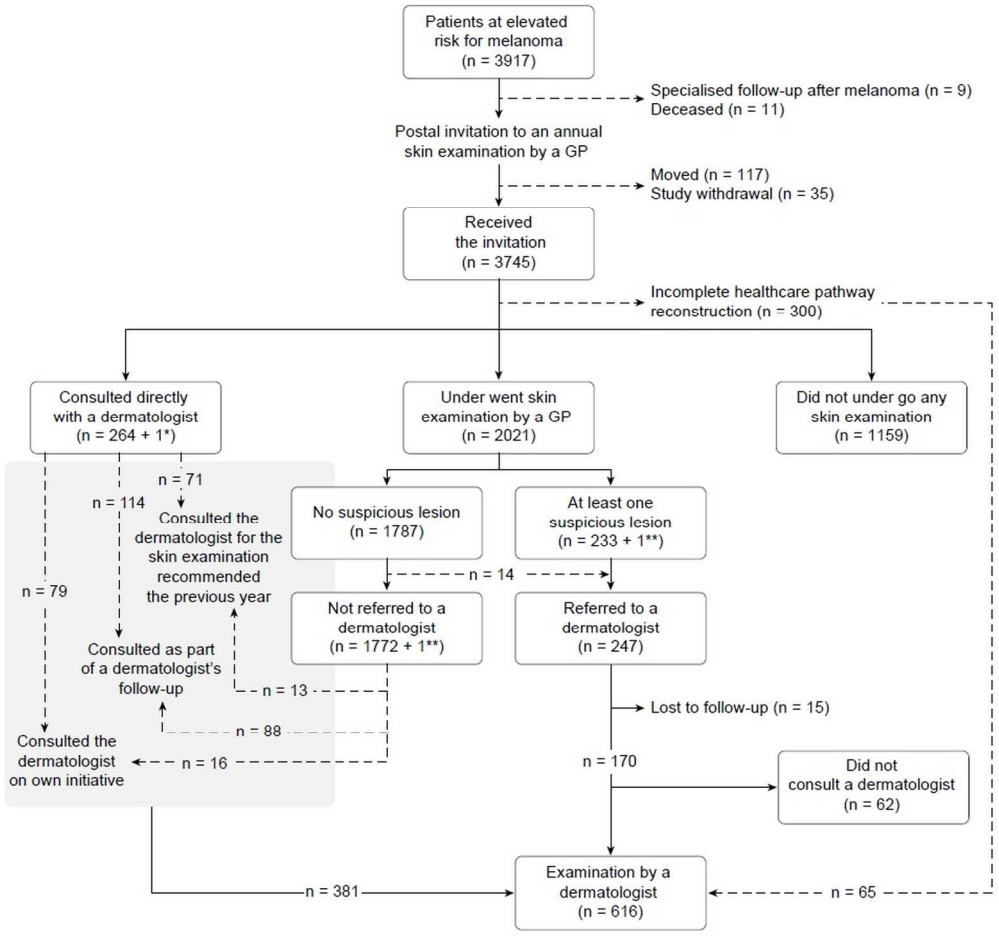

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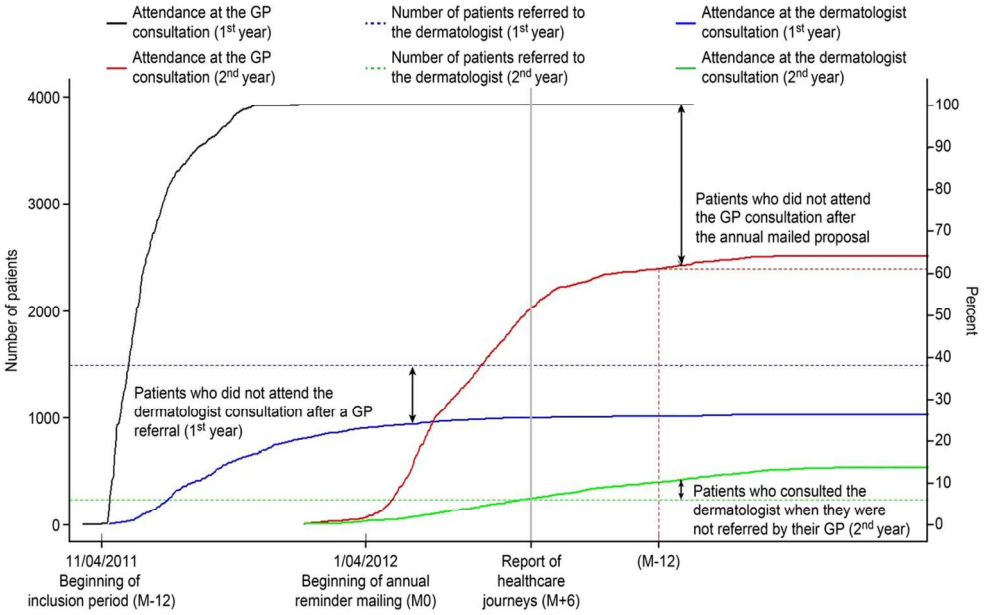

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Proposal for an annual skin examination by a general practitioner for patients at high risk for melanoma: A French cohort study.

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ABSTRACT

Objective: To evaluate the efficacy of a targeted screening for melanoma in high-risk patients following the receipt of a mailed invitation to an annual skin examination by a general practitioner (GP).

Methods: A prospective cohort study was conducted in a primary care setting in western France. A total of 3,897 patients at elevated risk of melanoma (identified using the Self-Assessment of Melanoma Risk Score) consented to participate in a targeted melanoma screening project in 2011. One year later, the participants were invited by mail to consult their GP for an annual skin examination. Efficacy of the procedure was evaluated according to patient participation and the number of melanomas detected. The consultation dates and results were collected during the 12 months post-reminder and were analysed using SAS. Analyses of whether participation decreased compared with that during the year of inclusion and whether populations at risk for thick melanoma showed reduced participation in the screening were performed.

Results: Of the 3,745 patients who received the mailed invitation, 61.0% underwent a skin examination. The participation of patients at risk for thick melanoma (any patient over 60 years of age and men over 50 years of age) was significantly greater than that of the patients in the other subgroups (72.4% vs. 49.6%, p<0.001; and 66.0% vs. 52.4%, p<0.001, respectively). The patients referred to the dermatologist after one year were more compliant compared with those referred during the first year (68.8% vs. 59.1%, p=0.003). Six melanomas were detected within one year post-reminder; therefore, the incidence of melanoma in the study population was 160/100,000.

Conclusion: This study confirms the benefits of developing a targeted screening strategy in primary care. In particular, after the annual reminder, patient participation and the diagnosis of melanoma remained high in the patients at elevated risk of thick melanomas.

Keywords: melanoma; screening; early detection of cancer; primary healthcare

Registration number: NCT01610531

ARTICLE SUMMARY

Strengths and limitations of this study

- The study was conducted in a primary care setting.
- The participants were patients at elevated risk of melanoma who were recruited using a validated and reproducible procedure based on the Self-Assessment of Melanoma Risk Score.
- Six months after receiving an annual reminder to consult their general practitioner for a targeted screening for melanoma, 61.0% of the patients underwent a skin examination.
- The participation of patients at risk for thick melanoma was significantly above average.
- Six melanomas were detected. These results yielded a crude melanoma incidence of 160/100,000 in the cohort population and 469/100,000 in the men older than 50.

INTRODUCTION

In France, the incidence of melanoma is estimated at 10.8/100,000 for men and 11.0/100,000 for women [1]. Overall, the incidence increased by 3.5 between 1980 and 2012 [1]. Because the lesions are visible, they should be detected at an early stage through skin examination. However, in 2012, melanoma was responsible for 1,672 deaths in France [1]. The main prognostic factor is the Breslow thickness (in millimetres) at the time of diagnosis [2]. The 5-year survival rate of patients with localised melanoma is 98.1%, compared with only 16.1% for metastatic melanoma patients [3]. Despite these findings, routine screening by full skin examination is not recommended in France [4], the United States [5], Australia or New Zealand, although the latter has the highest incidence of this disease worldwide [6,7]. Indeed, the efficacy of routine screening in decreasing the mortality rate for these patients has not been proven [5], and routine screening would be expensive to perform [8].

Conducting targeted screenings based on the identification of high-risk subjects could be a more valuable [9] and cost-effective strategy [8,10,11]. The following main risk factors for melanoma are well known [12–14]: a personal or family history of melanoma, the presence of greater than 40 nevi, the presence of atypical nevi, skin phenotype I or II, freckles and actinic damage, and a history of sunburns. Certain demographic groups have also been identified as being at higher risk of *thick* melanoma [9,15], including men, individuals over 60 years of age [16,17], and men over 50 years of age [18]. However, there is a need to define the best way to identify, screen, and follow individuals at high-risk of primary cutaneous melanoma [19].

A low physician density has also been associated with the identification of thick melanomas [20–22]. Melanomas tend to be thinner when they are detected by physicians rather than patients and also when they are detected during screening skin examination

rather than during routine care [17,23–27]. However, only 20% of patients who have had melanoma report that they previously consulted a dermatologist [28]. Therefore, general practitioners (GPs) could play a significant role in the screening of these patients. One study has reported that the proportion of melanomas diagnosed by GPs in France increased from 24% in 2004 to 42% in 2008 following the implementation of a system requiring patients to register their attending physician [29].

Based on these findings, our team has developed a targeted melanoma screening procedure grounded in primary care, using the Self-Assessment of Melanoma Risk Score (SAMScore). This score is based on a 7-item self-administered questionnaire (Figure 1) that a patient can answer without specific medical knowledge (30-32) and allows for the selection of a population at high risk of melanoma during primary care consultations [30–33]. The SAMScore algorithm allows for the expression of risk in a dichotomous format (either at elevated risk or not for melanoma) (Figure 1). According to the SAMScore, a patient is considered at elevated risk for melanoma if at least one of the following 3 criteria is met: 1) the presence of at least 3 risk factors among the following 7 risk factors: phenotype I or II, a freckling tendency, >20 melanocytic nevi on both arms, experienced severe sunburn during the childhood or teenage years, resides in a country at low latitude, a history of previous melanoma, and a history of melanoma in a first-degree relative; 2) under 60 years of age and >20 melanocytic nevi on both arms; and 3) sixty years of age or older with a freckling tendency. Previous research based on a literature review has suggested a relative risk of 13.77 in the selected high-risk population [31-32]. The SAMScore has been used to create a cohort of patients at high risk of melanoma (COPARIME) who were then asked to participate in a pilot targeted screening for melanoma (NCT01610531) [33]. The targeted melanoma screening procedure comprised the following 3 steps: 1) identifying high-risk patients using the SAMScore; 2) asking GPs to perform a total skin examination on these high-risk patients; and 3) referring patients to

a dermatologist if needed (for patients requiring a specialist opinion according to the GP). Between April and October 2011, 3,917 patients were included, nine of whom had melanoma. The crude incidence observed during the first year of screening (229/100,000) highlighted the potential benefit of such a targeted screening [33].

However, the generalizability of the findings based on a one-year intervention might be low. A major issue is the compliance of high-risk patients selected by the SAMScore who would be asked to consult yearly for melanoma screening and to consult a dermatologist in the case of a suspicious lesion [34]. Specific attention should be paid to patients at high risk of *thick* melanoma (including men, individuals over 60 years of age and men over 50 years of age) because their concern for melanoma screening has been reported to be lower compared with other high-risk patients [16-18].

Our team contacted all patients at risk of melanoma from the COPARIME cohort at one year after their inclusion in the targeted screening procedure. They received a mailed invitation to reconsult their GP for an annual skin examination. The aim of the study was to evaluate the efficacy of the mailed reminder, based on the following two variables: patient participation (with a specific focus on populations at risk of thick melanoma) and the number of melanomas detected.

METHODS

Design of the study

This study was based on a prospective follow-up of the COPARIME cohort. The patients were initially enrolled between April 11 and October 30, 2011, by 78 GP volunteers in western France, specifically in the departments of Loire-Atlantique and Vendée. All dermatologists in both departments participated in the study. The dermatologist density is 5.3/100,000 inhabitants in Loire-Atlantique, a predominantly urban department, and 2.1/100,000 inhabitants in Vendée, a more rural department. These physician densities are comparable to those of other French departments (national mean: 5.3/100,000) [35].

Participants

The eligibility criteria to receive the reminder at one year were as follows: being at high risk for melanoma according to the SAMScore, having agreed to participate in the targeted melanoma screening one year earlier, being over 18, and having no personal history of melanoma. Twenty patients were excluded from the COPARIME database, including 9 who had developed melanoma during the year since initially participating and had been directly recommended for a dermatologist follow-up and 11 who had died. As a result, a total of 3,897 patients were eligible (Figure 2).

Annual skin examination by general practitioner

An invitation to reconsult their GP for an annual skin examination was sent to eligible patients by mail at one year after their inclusion in the cohort.

The GP was asked to perform a total skin examination. Patients were referred to a dermatologist based on the opinion of the GP (as in routine care). The dermatologists were asked to classify their examinations of these referred patients according to the following three categories: “benign lesion”, “lesion to monitor” and “indication for exeresis”. When exeresis was indicated, the last step was anatomopathological examination.

Data collection

In addition to sending a reminder to the patients, each GP was mailed a table summarising the following data to be collected for each patient: the date of skin examination, the identification or not of a suspicious lesion, and whether the patient was referred to a dermatologist. An updated table was sent to the GPs at months 6 and 12. If data were missing at one year after sending the reminder, an investigator contacted the GP by telephone and offered to visit the medical practice to facilitate data collection.

One year after the reminder was mailed to the last patient in the cohort, each dermatologist was mailed a table summarising the data to be collected for each patient, including the date of the dermatological consultation and the conclusion derived from the skin examination, i.e., “benign lesion”, “lesion to monitor”, or “indication for exeresis”. The anatomopathological result was also recorded when available. If data were missing, an investigator contacted the dermatologist by telephone and offered to visit the medical practice.

Between June and December 2013, all patients for whom no data were available were recontacted to determine whether they had consulted a dermatologist. All of the data collected during these telephone calls with patients were then confirmed or invalidated based on data from a physician (GP or dermatologist).

All of the data were recorded in an Access database.

Efficacy: patient participation and number of melanomas detected

Participation in the follow-up annual skin examination by the GP was assessed at 6 months after mailing the invitation.

Patient participation following the mailing of the invitation was analysed after the classification of the patients into the following 6 categories: 1) underwent the skin examination by the GP as expected; 2) directly consulted a dermatologist without reconsulting the GP, even though he/she had not consulted a dermatologist when his/her GP had referred him/her the previous year; 3) directly reconsulted his/her dermatologist as part of his/her dermatological follow-up; 4) directly reconsulted his/her dermatologist on his/her own initiative; 5) had no skin examination by his/her GP and no dermatological consultation; and 6) was referred to a dermatologist following examination by his/her GP but did not consult the dermatologist.

Melanoma cases were described using pathological reports.

Statistical analysis

Quantitative data are presented as the mean and median. Subgroup analysis was performed for the men, patients over 60 years of age, men over 50 years of age, and patients living in rural areas. Data from the first year were compared with data from the second year using the Chi-square and Fisher's exact tests. The GP effect was tested using a Fisher variance ratio test. Statistical significance was set at 0.05. R 3.10.0 software was used.

Opinion of the ethics committee

The ethics committee of Tours University Hospital has given its favourable opinion on the performance of the study (n°2011-R2-BRD 10/11-N).

RESULTS

Patient demographics

Of the 3,897 patients, 117 moved without leaving a forwarding address, and 35 discontinued their participation in the study, leaving 3,745 patients for integration into analysis. The mean age of the patients was 44.5 (±15.6) years, and there were 1,197 (32%) men. In total, 713 (19%) patients were over 60 years of age, and 426 (11.3%) were men over 50 years of age. Finally, 2,427 (64.8%) patients lived in Loire-Atlantique, 1,206 (32.2%) in Vendée, and 112 (3.25%) in other departments.

Patient participation

After the one-year follow-up, 61% of the patients included in the targeted screening procedure reconsulted their GP, and 16% reconsulted a dermatologist (Figure 3). A total of 17.1% of the cohort patients were lost to follow-up.

Figure 2 shows the 6 methods of patient participation, analysed at 6 months after the invitation was mailed to reconsult. A total of 264 (7%) patients directly consulted a dermatologist, 2,021 (54%) reconsulted their GP, and 1,159 (31%) had no skin monitoring.

The proportion of referred patients who actually consulted a dermatologist increased after the reminder at one year compared with that upon initial inclusion in the screening (68.8% vs. 59.1%, $p<0.001$). However, the overall proportion of cohort patients who consulted a dermatologist was lower (15.8% vs. 23.9%, $p<0.001$) because the proportion of patients referred to a dermatologist by the GPs was lower (12.2% vs. 38.3%, $p<0.001$) (Table 1). The GP effect, tested as a random factor for the corresponding variables, was not significant ($p=0.10$ and $p=0.32$, respectively).

Melanoma cases

A total of 83 patients underwent exeresis, and 6 melanomas, 5 squamous cell carcinomas and 15 basal cell carcinomas were diagnosed. The characteristics of the 6 melanomas are provided in Table 2. Of the 6 melanomas, 5 were identified among the patients initially referred by their GP. The incidence of melanoma standardised to the populations of both departments was $183.7/10^5$ for men and $98.7/10^5$ for women.

The median thickness of the melanomas detected during the second year was 0.405 mm (Table 2). One melanoma was greater than 1 mm thick, which was identified in a patient who had not consulted a dermatologist after having been referred the first year.

In men over 50 years of age, the exeresis rate (21.0% vs. 11.6%, p=0.029) and the number of malignant lesions identified after exeresis (66.7% vs. 21.5%, p<0.001) were higher compared with the reference group (Table 3). In patients over 60 years of age, the number of malignant lesions identified after exeresis (66.7% vs. 19.4%, p<0.001) was higher compared with the reference group (Table 3).

DISCUSSION

Main results

Six months after receiving the annual reminder to schedule a total skin examination with their GP, 61.0% of the patients underwent a skin examination. Of them, 7.1% directly consulted a dermatologist. Of the patients who consulted their GP, 12.2% were referred to a specialist. The participation of populations at risk for thick melanoma was significantly above average. Six new melanomas were detected, corresponding to a crude incidence of 160/100,000.

Strengths and weaknesses

The strengths of this study are the size of the study population, the screening procedure initiated under primary care and under real care conditions, the use of a single validated and reproducible tool to detect high-risk subjects, and the prospective follow-up of the cohort.

This study also has certain limitations, including the number of patients lost to follow-up, the inclusion bias (women and young subjects were over-represented in the population) and the absence of data on the false negative rate of the procedure. Female over-representation is usually found in skin screening programs [36–39] and more generally in cancer screening [40,41]. This bias could also be related to the population seeking consultation in general practice, which is not entirely representative of the general population [33,42].

Last but not least, this study was conducted in a French setting and involved GPs who were volunteers; thus, the generalizability of the findings should be considered with caution. The study design was grounded in a healthcare system in which GPs have a

mission of regulating access to secondary care. This organisation has been implemented in a large majority of European countries [43]. However, national specificities may affect the referral and management procedures. Other variations may also appear in relation to discrepancies in the use of dermoscopy.

Interpretation of the results and comparison with data from the literature

The 61.0% rate of participation in the annual skin examination is higher than the rates observed for other cancers in France, including 52.1% for mammography [44], 34.3% for Hemoccult II [45] and 58.7% for cervical smear [46]. This good participation rate, observed after the one-year reminder, is a significant result that indicates the success of the screening. Offering a targeted screening rather than a screening of the general population could be associated with better participation.

Six melanomas with a median Breslow thickness of 0.405 mm were diagnosed during the second year of follow-up, and only one melanoma was greater than 1 mm thick. Similarly, other authors have reported that screening procedures help to identify predominantly thin lesions with a median Breslow thickness of approximately 0.3 mm [32,47,48]. The standardised incidence of melanoma in the high-risk population in this study was much higher than that which has been established in this geographic area (7.9 and 3.7 times higher for men and women, respectively). This increased incidence confirms that identifying patients at elevated risk of melanoma is relevant. This result is novel because most studies have only reported the benefit of a screening procedure immediately after the intervention. The observation of transient over-detection in these studies did not allow for an assessment of the benefit that would have been obtained if the screening procedure had been extended [32,33,49].

The present study confirms the potential benefit of GP consultation. First, 5 of the 6 new melanoma cases were identified among patients referred by their GP. Second, the concentration effect related to GP consultation was increased. Indeed, the proportion of patients referred to a dermatologist by their GP decreased during the second year compared with the first year (12.2% vs. 38.3%). This proportion is more consistent with previously published data that have revealed proportions of referred patients ranging from 7.4% to 26% [36,50–52]. This evolution could be explained by the need for GPs to perform an initial dermatologist reference examination during the year of inclusion, whereas their role would subsequently be to ensure the absence of evolution of pre-existing lesions.

The benefit of the proposed screening seemed the highest in the populations at risk of thick melanoma. Men, subjects over 60 years of age, and men over 50 years of age accounted for 32%, 19% and 11.3% of the cohort population, respectively, but they accounted for 50%, 50% and 33% of the melanoma patients, which is consistent with the findings of other authors [18,51,53]. No very thick melanomas (> 3 mm) were detected in our high-risk population over the course of two years. We were not able to conclude whether this result was due to the efficacy of the screening procedure or if it was simply related to the low incidence of thick melanomas in the population. The only melanoma greater than 1 mm was paradoxically detected during the second year: the corresponding patient had been referred to a dermatologist during the first year, but he did not consult the dermatologist until more than one year later. For this type of minimally compliant patient, our mailed reminder could have communicated to the patient that he or she was responsible for any appointment made. Thus, the benefits of a primary care-based targeted screening on the incidence of very thick melanomas could be due to not only the involvement of GPs

trained in screening [52] but also the impact of a simple annual reminder on minimally compliant patients.

Finally, 95 patients consulted a dermatologist on their own initiative, one of whom had a melanoma. This finding is consistent with the results of other studies showing that certain subjects participating in skin screening programs appropriately pursue consultations on their own [36,49,54-57]. In our study, it is likely that patients who were sensitised to their risk status and educated in skin self-examination by their GP directly consulted a dermatologist when they identified a suspicious lesion.

Practical implications and perspectives

In our study, we evaluated a generic procedure that addresses the reported limits of numerous national guidelines [19]. The identification of high-risk individuals was based on a validated tool. We assessed a reproducible procedure for the clinical management of individuals defined as high risk, involving the mailing of a yearly invitation for a clinical skin examination performed by a GP.

More than half of the patients identified as being at risk for melanoma according to the SAMScore responded positively to our mailed reminder about scheduling an annual skin examination with their GP. The high melanoma incidence and low melanoma thickness identified in this study are both in favour of a targeted screening conducted in primary care.

Extending the follow-up of our cohort would allow for an assessment of the proportion of false negatives related to GPs' examinations. Other major issues that should be addressed include assessments of the follow-up pace to be proposed in this population and the related

costs. The validation of a beneficial effect of this screening procedure on mortality will require a randomised study.

Ethical approval

The ethics committee of the University Hospital of Tours approved this study (n° 2011-R2-BRD 10/11-N).

STATEMENTS

a. CONTRIBUTORSHIP STATEMENT

CR conceived of the study, participated in its design and supervision, and was responsible for the GP network and for drafting the manuscript. CG participated in the design of the study, was responsible for the data collection, and helped to draft the manuscript. GQ participated in the design of the study, managed the pathological reports, and helped to draft the manuscript. MD participated in the data collection and helped to draft the manuscript. AG performed statistical analysis and helped to draft the manuscript. AK and BD participated in the design, were responsible for the dermatologist network, and provided administrative and technical support. JMN participated in the design of the study, was responsible for statistical analysis and study supervision and helped to draft the manuscript. All authors read and approved the final manuscript.

b. COMPETING INTERESTS

None reported. The sponsor (French National Institute of Cancer) had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

c. FUNDING

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d. DATA SHARING STATEMENT

No additional data available

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REFERENCES

1 Binder-Foucard F, Belot A, Delafosse P, et al. Estimation nationale de l'incidence et de la mortalité par cancer en France entre 1980 et 2012. Partie 1 - Tumeurs solides. Saint-Maurice (Fra): Institut de Veille Sanitaire 2013.

2 Balch CM, Gershenwald JE, Soong S-J, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol Off J Am Soc Clin Oncol 2009;**27**:6199–206.

3 How Many People Survive 5 Years Or More after Being Diagnosed with Melanoma of the Skin? http://seer.cancer.gov/statfacts/html/melan.html#survival (accessed 10 Sep2014).

4 Haute Autorité de Santé. Stratégie de diagnostic précoce du mélanome. 2006.www.has-sante.fr/

5 U.S. Preventive Services Task Force. Screening for skin cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009;**150**:188–93.

6 Cancer Council Australia, New Zealand, Ministry of Health, et al. Clinical practice guidelines for the management of melanoma in Australia and New Zealand: evidence-based best practice guidelines. Sydney, N.S.W.; New Zealand: : Cancer Council Australia : Australia Cancer Network ; Ministry of Health 2008.

7 Bray F, Ren J-S, Masuyer E, et al. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 2013;**132**:1133–45.

8 Losina E, Walensky RP, Geller A, et al. Visual screening for malignant melanoma: a cost-effectiveness analysis. Arch Dermatol 2007;**143**:21–8.

9 Curiel-Lewandrowski C, Chen SC, Swetter SM, et al. Screening and prevention measures for melanoma: is there a survival advantage? Curr Oncol Rep 2012;**14**:458–67.

10 Freedberg KA, Geller AC, Miller DR, et al. Screening for malignant melanoma: A cost-effectiveness analysis. J Am Acad Dermatol 1999;**41**:738–45.

11 Gordon LG, Rowell D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP Published Online First: 2 August 2014.

12 Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur J Cancer Oxf Engl 1990 2005;**41**:28–44.

13 Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer Oxf Engl 1990 2005;**41**:45–60.

14 Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur J Cancer Oxf Engl 1990 2005;**41**:2040–59.

15 Geller AC, Swetter SM, Oliveria S, et al. Reducing mortality in individuals at high risk for advanced melanoma through education and screening. J Am Acad Dermatol 2011;**65**:S87–94.

16 Geller AC, Elwood M, Swetter SM, et al. Factors related to the presentation of thin and thick nodular melanoma from a population-based cancer registry in Queensland Australia. Cancer 2009;**115**:1318–27.

17 Swetter SM, Pollitt RA, Johnson TM, et al. Behavioral determinants of successful early melanoma detection: role of self and physician skin examination. Cancer 2012;**118**:3725–34.

18 Geller AC, Sober AJ, Zhang Z, et al. Strategies for improving melanoma education and screening for men age >or= 50 years: findings from the American Academy of Dermatological National Skin Cancer Sreening Program. Cancer 2002;**95**:1554–61.

19 Watts CG, Dieng M, Morton RL, Mann GJ, Menzies SW, Cust AE. Clinical practice guidelines for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma: a systematic review. Br J Dermatol. 2015;**172**:33-47.

20 Van Durme DJ, Ullman R, Campbell RJ, et al. Effects of physician supply on melanoma incidence and mortality in Florida. South Med J 2003;**96**:656–60.

21 Stitzenberg KB, Thomas NE, Dalton K, et al. Distance to diagnosing provider as a measure of access for patients with melanoma. Arch Dermatol 2007;**143**:991–8.

22 Aneja S, Aneja S, Bordeaux JS. Association of increased dermatologist density with lower melanoma mortality. Arch Dermatol 2012;**148**:174–8.

23 Helfand M, Mahon SM, Eden KB, et al. Screening for skin cancer. Am J Prev Med 2001;**20**:47–58.

24 Epstein DS, Lange JR, Gruber SB, et al. Is physician detection associated with thinner melanomas? JAMA J Am Med Assoc 1999;**281**:640–3.

25 McPherson M, Elwood M, English DR, et al. Presentation and detection of invasive melanoma in a high-risk population. J Am Acad Dermatol 2006;**54**:783–92.

26 Aitken JF, Elwood M, Baade PD, et al. Clinical whole-body skin examination reduces the incidence of thick melanomas. Int J Cancer J Int Cancer 2010;**126**:450–8.

27 Richard MA, Grob JJ, Avril MF, et al. Delays in diagnosis and melanoma prognosis (II): the role of doctors. Int J Cancer J Int Cancer 2000;**89**:280–5.

28 Geller AC, Koh HK, Miller DR, et al. Use of health services before the diagnosis of melanoma: implications for early detection and screening. J Gen Intern Med 1992;**7**:154–7.

29 Grange F, Barbe C, Mas L, et al. The role of general practitioners in diagnosis of cutaneous melanoma: a population-based study in France. Br J Dermatol 2012;**167**:1351–9.

30 Quéreux G, Nguyen J-M, Volteau C, et al. Creation and test of a questionnaire for self-assessment of melanoma risk factors: Eur J Cancer Prev 2010;**19**:48–54.

31 Quéreux G, Moyse D, Lequeux Y, et al. Development of an individual score for melanoma risk: Eur J Cancer Prev 2011;**20**:217–24.

32 Quéreux G, Nguyen J-M, Cary M, et al. Validation of the Self-Assessment of Melanoma Risk Score for a melanoma-targeted screening. Eur J Cancer Prev 2012;**21**:588–95.

33 Rat C, Quereux G, Grimault C, et al. Melanoma incidence and patient compliance in a targeted melanoma screening intervention. One-year follow-up in a large French cohort of high-risk patients. Eur J Gen Pract 2014:1–7.

34 Rat C, Quereux G, Monegier du Sorbier M, et al. Patients at elevated risk of melanoma: individual predictors of non-compliance to GP referral for a dermatologist consultation. Prev Med 2014;**64**:48–53.

35 Démographie médicale interactive | Démographie médicale. Cons. Natl. Médecins. http://demographie.medecin.fr/demographie (accessed 13 Sep2014).

36 Breitbart EW, Waldmann A, Nolte S, et al. Systematic skin cancer screening in Northern Germany. J Am Acad Dermatol 2012;**66**:201–11.

37 Andrulonis R, Secrest AM, McGuire ST, et al. The influence of age and sex on reasons for seeking and expected benefits of skin cancer screening. Arch Dermatol 2010;**146**:1097–102.

38 De Rooij MJ, Rampen FH, Schouten LJ, et al. Factors influencing participation among melanoma screening attenders. Acta Derm Venereol 1997;**77**:467–70.

39 Argenziano G, Zalaudek I, Hofmann-Wellenhof R, et al. Total body skin examination for skin cancer screening in patients with focused symptoms. J Am Acad Dermatol 2012;**66**:212–9.

40 Davis JL, Buchanan KL, Katz RV, et al. Gender differences in cancer screening beliefs, behaviors, and willingness to participate: implications for health promotion. Am J Mens Health 2012;**6**:211–7.

41 Sach TH, Whynes DK. Men and women: beliefs about cancer and about screening. BMC Public Health 2009;**9**:431.

42 Green LA, Fryer GE, Yawn BP, et al. The ecology of medical care revisited. N Engl J Med 2001;**344**:2021–5. doi:10.1056/NEJM200106283442611

43 Masseria C, Irwin R, Thomson S, Gemmill M, Mossialos E. Primary care in Europe. European Commission report. 2009.

44 Institut National de Veille Sanitaire (InVS). Evolution des taux de participation au programme national de dépistage organisé du cancer du sein par classe d'âge, depuis 2005. http://www.invs.sante.fr/fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Cancers/Evaluation-des-programmes-de-depistage-des-cancers/Evaluation-du-programme-de-depistage-du-cancer-du-sein/Indicateurs-d-evaluation/Evolution-des-taux-de-participation-au-programme-national-de-depistage-organise-du-cancer-du-sein-par-classe-d-age-depuis-2005 (accessed 22 Sep2014).

45 Leuraud K, Jezewski-Serra D, Viguier J, et al. Colorectal cancer screening by guaiac faecal occult blood test in France: Evaluation of the programme two years after launching. Cancer Epidemiol 2013;**37**:959–67.

46 Duport N. Données épidémiologiques sur le cancer du col de l'utérus - Etat des connaissances - Actualisation 2008. Institut de Veille Sanitaire 2008. http://opac.invs.sante.fr/doc_num.php?explnum_id=3243

47 Koh HK, Norton LA, Geller AC, et al. Evaluation of the American Academy of Dermatology's National Skin Cancer Early Detection and Screening Program. J Am Acad Dermatol 1996;**34**:971–8.

48 Carli P, De Giorgi V, Giannotti B, et al. Skin cancer day in Italy: method of referral to open access clinics and tumor prevalence in the examined population. Eur J Dermatol EJD 2003;**13**:76–9.

49 Stratigos A, Nikolaou V, Kedicoglou S, et al. Melanoma/skin cancer screening in a Mediterranean country: results of the Euromelanoma Screening Day Campaign in Greece. J Eur Acad Dermatol Venereol JEADV 2007;**21**:56–62.

50 Veronesi A, Pizzichetta MA, De Giacomi C, et al. A two-year regional program for the early detection of cutaneous melanoma. Tumori 2003;**89**:1–5.

51 Aitken JF, Janda M, Elwood M, et al. Clinical outcomes from skin screening clinics within a community-based melanoma screening program. J Am Acad Dermatol 2006;**54**:105–14.

52 Engelberg D, Gallagher RP, Rivers JK. Follow-up and evaluation of skin cancer screening in British Columbia. J Am Acad Dermatol 1999;**41**:37–42.

53 Waldmann A, Nolte S, Geller AC, et al. Frequency of excisions and yields of malignant skin tumors in a population-based screening intervention of 360,288 whole-body examinations. Arch Dermatol 2012;**148**:903–10.

54 Mc Gee R, Elwood M, Williams S, et al. Who comes to skin checks? N Z Med J 1994;**107**:58–60.

55 Koh HK, Geller AC, Miller DR, et al. Who is being screened for melanoma/skin cancer? Characteristics of persons screened in Massachusetts. J Am Acad Dermatol 1991;**24**:271–7.

56 Paoli J, Danielsson M, Wennberg AM. Results of the 'Euromelanoma Day' screening campaign in Sweden 2008. J Eur Acad Dermatol Venereol JEADV 2009;**23**:1304–10.

57 Rat C, Quereux G, Riviere C, et al. Targeted melanoma prevention intervention: a cluster randomized controlled trial. Ann Fam Med 2014;**12**:21–8.

LEGENDS

Figure 1. Questionnaire used for the Self-Assessment of Melanoma Risk Score.

Figure 2. Participation among patients at elevated risk of melanoma at 6 months after a mailed reminder for an annual GP skin examination.

Figure 3. Participation in skin examinations by GPs and dermatologists among patients at elevated risk of melanoma based on a two-year follow-up.

TABLES

Table 1. Patient participation in a pilot melanoma targeted screening after an annual mailed reminder.

	Year after annual reminder mailing		Year of inclusion		p
	%	*(n/N)*	%	*(n/N)*	
Proportion of included patients who attended the GP consultation	54.0	*(2021/3745)*	100.0	*(3917/3917)*	<0.001
Proportion of patients referred to a dermatologist	12.2	*(247/2021)*	38.3	*(1502/3917)*	<0.001
Proportion of referred patients who actually consulted the dermatologist	68.8	*(170/247)*	59.1	*(887/1502)*	0.003
Proportion of patients lost to follow-up	17.1	*(665/3897)*	2.6	*(102/3917)*	<0.001
Proportion of overall patients who had a dermatological skin examination	15.8	*(616/3897)*	23.9	*(938/3917)*	<0.001

Table 2. Characteristics of melanomas diagnosed during the 2-year follow-up of the COPARIME cohort.

	N°	Gender	Patient age at diagnosis	Healthcare pathway	Type	Localisation	Breslow index (mm)	Delay between GP consultation and excision (days)
1st year of COPARIME targeted screening	1	F	31	Compliant	SSM	Forearm	0.16	24
	2	F	73	Compliant	Dubreuilh	Face	0	49
	3	M	64	Compliant	SSM	Back	0.8	49
	4	M	40	Compliant	SSM	Forearm	0.49	54
	5	M	51	Compliant	SSM	Back	0.245	106
	6	M	75	Compliant	Dubreuilh	Forearm	0.18	108
	7	F	34	Compliant	SSM	Thigh	0.52	124
	8				SSM	Thigh	0.15	124
	9	F	55	Patient's own initiative	SSM	Forearm	0	154
	10	M	56	Patient's own initiative	SSM	Back	0	286
2nd year of COPARIME targeted screening	11	F	71	Compliant	SSM	Thigh	0.45	33
	12	M	66	Compliant	Dubreuilh	Face	0	137
	13	M	59	Compliant	SSM	Bottom	0.38	191
	14	F	68	Referred in 2011, consulted after 2012 reminder	SSM	Calf	1.11	512
	15	M	42	Patient's own initiative	SSM	Back	0.43	513
	16	F	32	Referred in 2011, consulted after 2012 reminder	SSM	Back	0.242	709

	Breslow index (mm)			Delay between GP consultation and excision (days)		
	1st year	2nd year	p	1st year	2nd year	p
Mean	0.25	0.43	0.33[a]	107.8	349	0.077[a]
Median	0.17	0.405	0.65[b]	107	351	0.15[b]

F: Female, M: Male

SSM: Superficial spreading melanoma

[a] Student's t test

[b] Fisher test

Table 3: Malignant lesions and participation in populations at elevated risk of advanced melanoma

	Men older than 50	Others	p	>60 years old	<60 years old	p
	% *(n/N)*	% *(n/N)*		% *(n/N)*	% *(n/N)*	
Proportion of included patients who attended the GP consultation	66.0 *(281/426)*	52.4 *(1740/3319)*	<0.001	72.4 (516/713)	49.6 (1505/3032)	<0.001
Proportion of patients referred to a dermatologist	11.4 *(32/281)*	12.4 *(215/1740)*	0.72	10.7 (55/516)	12.8 (192/1505)	0.24
Proportion of referred patients who actually consulted the dermatologist	87.5 *(27/32)*	66.5 *(143/215)*	0.067	70.9 (39/55)	68.2 (131/192)	0.83
Proportion of patients lost to follow-up	10.0 *(43/430)*	18.0 *(522/2900)*	<0.001	8.0 (62/775)	19.0 (603/3174)	<0.001
Proportion of overall patients who had a dermatological skin examination	19.0 *(81/426)*	16.1 *(535/3319)*	0.15	17.7 (126/713)	16.2 (490/3032)	0.36
Proportion of exeresis decision among dermatologist consultation	21.0 *(17/81)*	11.6 *(62/535)*	0.029	15.9 (20/126)	12.0 (59/490)	0.32
Proportion of malignant lesions among excised lesions	66.7 *(12/18)*	21.5 *(14/65)*	<0.001	66.7 (14/21)	19.4 (12/62)	<0.001
Crude incidence of melanoma	$469/10^5$	$120/10^5$	0.14	$420/10^5$	$99/10^5$	0.09

Answer each question by circling the corresponding option:

1. What phenotype of skin do you have?
   . Skin phenotype I: very fair skin, blond or red hair, light eyes (blue or green), never tan and always sunburn after sun exposure
   . Skin phenotype II: fair skin, blond or light-brown hair, light eyes (blue or green), usually sunburn
   . Skin phenotype III: deep skin, brown hair, light to medium eye colour
   . Skin phenotype IV: olive skin, dark-brown hair, brown eyes
   . Skin phenotype V: brown skin, black hair, black eyes
   . Skin phenotype VI: black skin, black hair, black eyes
2. Do you have freckles? Yes / No
3. Approximately how many moles do you have on both arms? More than 20 / Fewer than 20
4. Have you had one or more episodes of a severe blistering sunburn during your childhood or teenage years? Yes / No
5. Have you lived in a country where the level of sunshine is high (Africa, French West Indies, the southern United States, Australia, etc.) for more than one year? Yes / No
6. Have you been diagnosed with melanoma (a skin cancer arising in melanocytes, the skin cells that make skin pigment) in the past? Yes / No
7. Have any of your first-degree relatives (parents, children, brother or sister) ever had melanoma? Yes / No / Don't know

According to the SAMScore, a patient is considered at elevated risk for melanoma if at least one of the following 3 criteria is met:

. First criterion: The presence of at least 3 risk factors among the following 7 risk factors: skin phenotype I or II, a freckling tendency, >20 melanocytic nevi on both arms, experienced severe sunburn during their childhood or teenage years, residing in a country at low latitude, a history of previous melanoma, and a history of melanoma in a first-degree relative.

. Second criterion: Under 60 years of age and >20 melanocytic nevi on both arms.

. Third criterion: Sixty years of age or older and a freckling tendency.

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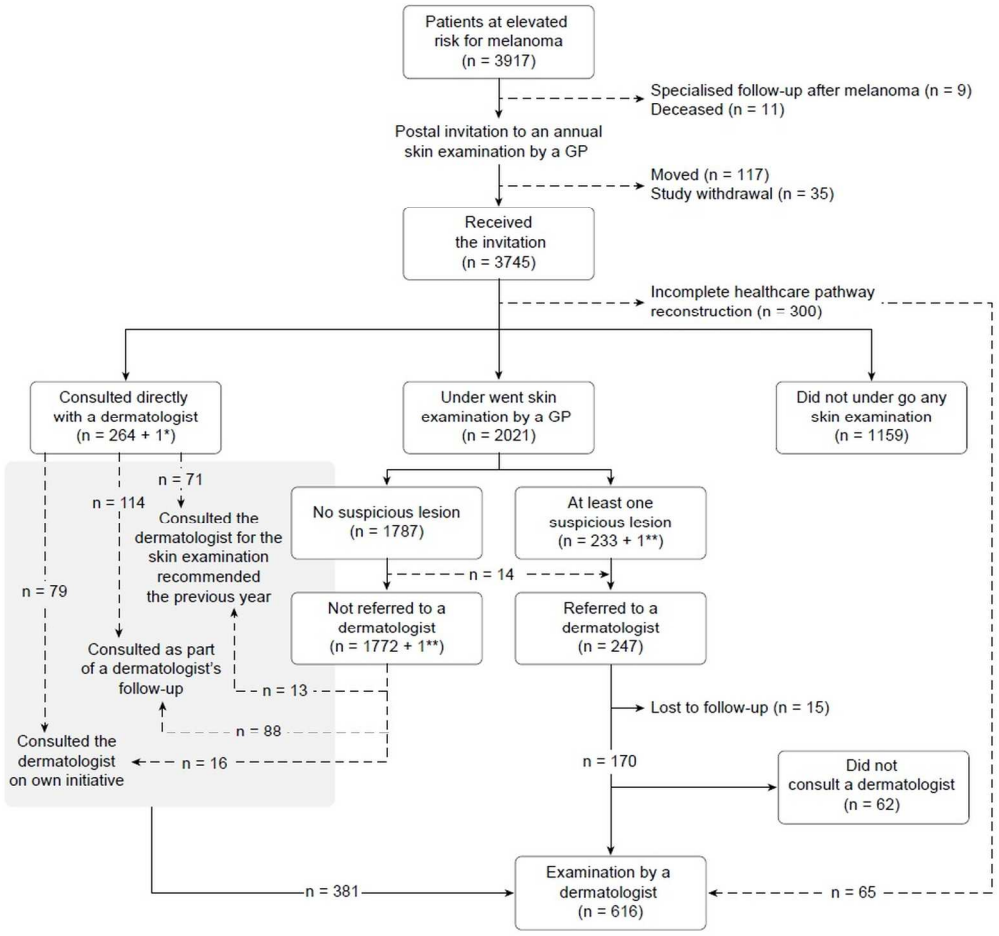

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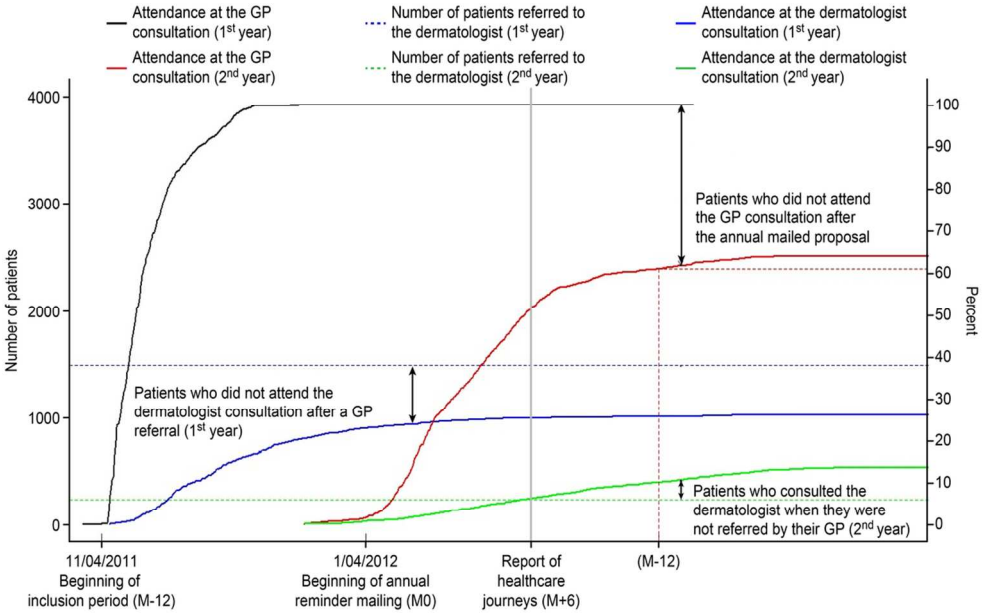

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