

Année 2020/2021

N°

Thèse

Pour le

DOCTORAT EN MEDECINE

Diplôme d'État

Par

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Née le 2 Juillet 1993 à BIARRITZ (64)

TITRE

**Fiche conseil pour améliorer l'adhésion à la détection précoce d'un
mélanome chez les apparentés au 1er degré d'un patient atteint de
mélanome : essai interventionnel randomisé en cluster**

Présentée et soutenue publiquement le **21 octobre 2021** devant un jury composé
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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

Remerciements

A Monsieur le Professeur Laurent Machet, merci pour m'avoir proposé de réaliser ce travail. A votre bienveillance, votre grande connaissance, votre altruisme, votre disponibilité, un grand merci pour l'accompagnement depuis le début de mon internat. A travers ce travail, veuillez trouver l'expression de mon admiration et de ma gratitude.

A Monsieur le Professeur Loïc Vaillant, merci de m'avoir fait l'honneur de faire partie du jury et d'en être le président. Vous avez su me transmettre votre passion pour la pathologie buccale.

A Madame le Professeur Annabel Maruani, merci pour ta pédagogie, ta grande rigueur, ta passion contagieuse pour la dermatologie pédiatrique. Tu as suscité une profonde admiration pour toutes tes compétences.

A Madame le Docteur Agnès Caille, sans qui cette étude n'aurait pu être réalisée, sans vos qualités et votre précieuse aide pour ce travail.

A Madame le Docteur Emmanuelle Le Bidre, merci pour ta disponibilité, ta gentillesse, le partage de ton savoir de la dermatologie. Un grand merci pour ton accompagnement depuis le début de mon internat.

A Madame le Professeur Mahtab Samimi, merci pour ta pédagogie, de partager cet amour pour la dermatologie. Trouve ici l'expression de mon plus profond respect et de ma gratitude.

A mes chefs de clinique, le Docteur Hélène Cornillier, le Docteur Margaux Garnier, merci pour tout ce que vous avez fait pour moi lors de mon premier semestre à Tours ; le Docteur Sophie Leducq et le Docteur Chakib El Habnoui.

A Madame le Docteur Cloé Corven, le Docteur Myriam Abdallah et le Docteur Martine Mauboussin, merci pour ce super stage à vos côtés, vous m'avez beaucoup appris.

A Madame le Docteur Valérie Tauveron,

A l'équipe de Rhumatologie de m'avoir enseigné avec passion votre spécialité dans la bonne humeur, ainsi que l'équipe de Maladies infectieuses d'Orléans.

A l'équipe d'Oncologie du CHU de Tours pour tout ce que vous m'avez apporté.

A Madame le Docteur Floriane Le Vilain-Abraham, pour votre précieuse aide pour ce travail.

A Céleste Verne et Stéphanie Bonte, merci pour votre implication si importante dans ce travail.

A toutes les équipes paramédicales de Dermatologie et d'Oncologie du CHU.

A mes co-internes de Dermatologie,

A Micka, Xing et Karole,

A Maya, Fanny et William,

A Léa, Florence, Manon, Sarah, Marine, Axelle, Auriane, Clémentine, Adriana, Pierre et
Timothée,

A Pierre et Louis,

A mes crossfat,

A Hélène,

A mes parents, Agathe, ma mamie, mon tatxi, mes tantes et mes cousins et cousines.

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Introduction générale

Le mélanome cutané malin (MM) est une tumeur maligne qui se développe à partir des mélanocytes et représente 4% de l'ensemble des cancers incidents[1] et 10 % des cancers de la peau[1]. Il représente 3,9% des cancers en Europe[2]. En France, il se situe au 8^{ème} rang des cancers chez l'homme et au 6^{ème} rang chez la femme[3]. Le risque de développer un MM pour la population générale au cours de toute une vie en France est estimé à 1,3 % chez l'homme et 1% chez la femme[4]. L'incidence du MM est en forte augmentation (triplement du risque ces trente dernières années), y compris chez les sujets jeunes, avec 15 513 nouveaux cas par an en France[4]. La mortalité liée au MM représente 1 975 décès/an en France[4]. Le pronostic vital est directement lié à l'épaisseur tumorale (plus de 90% de guérison si <1 mm versus 50% si plus de 4 mm) qui elle-même dépend de la vitesse de croissance tumorale[5] mais aussi du retard au diagnostic. Une densité faible en dermatologues et un retard d'accès aux soins sont associés à une épaisseur plus élevée des MM enlevés[6] et à une augmentation de la mortalité[7]. La surveillance régulière est associée à une réduction de l'épaisseur au moment de l'exérèse et à une diminution de la mortalité[8]. Des actions de prévention et de détection précoce en population générale en Australie ont montré une réduction de l'incidence par l'application de photo-protecteurs[9], et de l'épaisseur tumorale par la pratique d'un examen de détection précoce[10], mais restent coûteuses à grande échelle. Cependant, les coûts des traitements médicaux actuellement prescrits aux stades avancés ont nettement augmenté avec les options thérapeutiques modernes (60 000 à 120 000 euros pour une année de traitement adjuvant par patient) et rendent les programmes de prévention probablement plus rentables. De plus, il est très probable que les MM au stade II feront l'objet d'un traitement adjuvant d'une durée de 6 à 12 mois dans les 5 années à venir.

Le dépistage systématique n'est pas conseillé, mais celui des groupes à risque est recommandé. Ces groupes à risque plus élevé de survenue d'un MM sont les patients porteurs de nombreux naevus (>40 naevus communs), de naevus atypiques >2, de naevus congénital géant (diamètre >20cm), au phototype cutané clairs I et II, exposés aux UV (exposition intense et intermittente pendant l'enfance surtout), les patients immunodéprimés ou ayant des prédispositions génétiques au mélanome. Ainsi 10% des patients atteints d'un MM ont un apparenté au 1^{er} degré déjà atteint d'un MM. Le risque de MM est multiplié par 2 si 1 seul apparenté au 1^{er} degré est atteint d'un MM, et par 5 si 2 apparentés ou plus sont atteints[11–13]. Une étude médico-économique réalisée aux Etats-Unis avant l'ère des traitements médicaux modernes et onéreux a

estimé qu'une consultation bisannuelle est justifiée et « rentable » pour les apparentés au 1^{er} degré[14]. Il est donc conseillé aux apparentés au 1^{er} degré des patients ayant eu un MM d'adopter des mesures de photo-protection et de détection précoce (auto-examen cutané une fois par trimestre et consultation du dermatologue ou d'un médecin généraliste en vue d'un examen annuel complet de la peau). Ces conseils sont prodigués oralement par le dermatologue aux patients pris en charge pour un MM, qui sont invités à relayer l'information à leurs apparentés. Il n'existe pas à ce jour de support écrit national en France, destiné spécifiquement aux apparentés au 1^{er} degré d'un patient atteint de MM. L'absence de support écrit destiné aux apparentés est considérée comme un frein à la communication par 49% des dermatologues interrogés aux USA[15].

Nous avons mené au CHU de Tours une étude rétrospective évaluant l'utilité d'une fiche brève (½ page format A4) remise aux patients atteints d'un MM, contenant des conseils de photo-protection et de dépistage destinés à eux-mêmes et à leurs apparentés au 1^{er} degré. L'étude consistait en un recueil d'un auto-questionnaire remis aux patients et s'était déroulée pendant 3 périodes : 1998 (conseils oraux sans remise d'une fiche écrite aux patients), 2005 (conseils oraux avec remise systématique de la fiche), 2012 (conseils oraux et remise inconstante de la fiche). La remise d'une fiche écrite en 2005 à tous les patients a été associée à une meilleure adhésion au dépistage familial du MM déclaré par les patients (62% en 1998, 83,5% en 2005). Mais en 2012, la fiche n'était plus remise qu'à 16% des patients, et le dépistage familial ne concernait plus que 56% des patients ($p=0,002$). De plus, en 2012, l'adhésion au dépistage familial était plus élevée dans le sous-groupe qui avait reçu la fiche écrite, que dans le sous-groupe qui n'avait pas reçu la fiche (87,5 % versus 50,5 % pour ceux qui ne l'avaient pas reçue, $p=0,006$)[16]. La principale limite de cette étude, outre le fait qu'elle soit observationnelle, est que l'information a été recueillie auprès du sujet index ayant eu un MM, sans preuve directe auprès de ses apparentés de la véracité de la transmission de l'information par le patient à ses apparentés, puis à une mise en œuvre réelle de la détection précoce (par un auto-examen ou une consultation chez un dermatologue).

Les résultats de notre étude pilote nous ont incité à proposer un essai interventionnel randomisé pour évaluer de manière rigoureuse l'impact de la remise d'une fiche de conseils écrits, en plus des conseils usuels, donnés oralement. L'objectif principal de la présente étude est de mesurer la modification du comportement de détection précoce (réalisation d'un examen médical de la peau) des apparentés au 1^{er} degré (AP1D) suite à la remise d'une fiche-conseil associée à un conseil oral à des patients ayant un MM par comparaison à un conseil oral seul.

Les objectifs secondaires sont d'évaluer les modifications du comportement de photo-protection et la réalisation d'un auto-examen cutané par les AP1D suite à la remise d'une fiche-conseil associée à un conseil oral à des patients ayant un MM, par comparaison à un conseil oral seul.

Références :

1. e-cancer. Epidémiologie des cancers cutanés - Détection précoce des cancers de la peau [Internet]. Available from: <https://www.e-cancer.fr/Professionnels-de-sante/Depistage-et-detection-precoce/Detection-precoce-des-cancers-de-la-peau/Epidemiologie>
2. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer*. 2018;103:356–87.
3. cancer-environnement.fr. Mélanome cutané | Cancer et environnement [Internet]. [cited 2021 Aug 30]. Available from: <https://www.cancer-environnement.fr/340-Melanome-cutane.ce.aspx>
4. e-cancer. Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018. Volume 1 – Tumeurs solides. :372.
5. Grob JJ, Richard MA, Gouvernet J, Avril MF, Delaunay M, Wolkenstein P, et al. The kinetics of the visible growth of a primary melanoma reflects the tumor aggressiveness and is an independent prognostic marker: A prospective study. *Int J Cancer*. 2002;102:34–8.
6. Duberc F, Vitry F, Granel-Brocard F, Lipsker D, Aubin F, Hédelin G et al. The role of circumstances of diagnosis and access to dermatological care in early diagnosis of cutaneous melanoma: A population-based study in France. *Arch Dermatol*. 2010;146:240-246.
7. Aneja S, Aneja S, Bordeaux JS. Association of increased dermatologist density with lower melanoma mortality. *Arch Dermatol*. 2012;148:174-8.
8. Carli P, De Giorgi V, Palli D, Maurichi A, Mulas P, Orlandi C, et al. Dermatologist detection and skin self-examination are associated with thinner melanomas: results from a survey of the Italian Multidisciplinary Group on Melanoma. *Arch Dermatol*. 2003;139:607-12.
9. Green AC, Williams GM, Logan V, Strutton GM. Reduced Melanoma After Regular Sunscreen Use: Randomized Trial Follow-Up. *J Clin Oncol*. 2011;29:257–63.
10. Aitken JF, Elwood M, Baade PD, Youl P, English D. Clinical whole-body skin examination reduces the incidence of thick melanomas. *Int J Cancer*. 2010;126:450–8.
11. Balch C. An analysis of prognostic factors in 8500 patients with cutaneous melanoma. *Cutaneous melanoma*. Lippincott; 1992;163–87.
12. Ford D, Bliss JM, Swerdlow AJ, Armstrong BK, Franceschi S, Green A, et al. Risk of cutaneous melanoma associated with a family history of the disease. *Int J Cancer*. 1995;62:377–81.
13. Rhodes AR, Weinstock MA, Fitzpatrick TB, Mihm MC, Sober AJ. Risk factors for cutaneous melanoma. A practical method of recognizing predisposed individuals. *JAMA*. 1987;258:3146–54.
14. Losina E, Walensky RP, Geller A, Beddingfield FC, Wolf LL, Gilchrist BA, et al. Visual screening for malignant melanoma: a cost-effectiveness analysis. *Arch Dermatol*. 2007 ;143:21-8.
15. Oliveria SA, Heneghan MK, Halpern AC, Hay JL, Geller AC. Communication About Family Members' Risk of Melanoma: Self-reported Practices of Dermatologists in the United States. *Arch Dermatol* . 2012;148:621–7.
16. Berton M, Perrinaud A, Samimi M, Delaplace M, Vaillant L, Machet L. Utilité d'une fiche de conseils pour la photoprotection et le dépistage des patients et de leur famille après un diagnostic de mélanome. *Ann Dermatol Venerol* 2013 ; 140 : S407-408.

Résumé en Français

Rationnel :

Les apparentés au premier degré (AP1D) définis comme les parents, les enfants et les frères et sœurs, des patients atteints de mélanome cutané malin (MM) ont un risque 2 à 5 fois plus élevé de développer eux-mêmes un MM. Il est donc conseillé aux AP1D des patients atteints, d'adopter des mesures de photo-protection et de détection précoce du MM (auto examen de la peau et consultation annuelle chez un dermatologue ou un médecin généraliste). Ces conseils sont donnés oralement par le médecin aux patients pris en charge pour un MM qui sont alors invités à relayer l'information à leurs apparentés.

Hypothèses et objectifs :

Notre objectif était de déterminer dans un essai contrôlé randomisé en cluster (ClinicalTrials NCT02917473), l'impact de la remise d'une fiche conseil aux patients atteints de MM et destinée à leur AP1D sur les comportements de détection précoce du MM et de photo-protection. Notre hypothèse était que la fiche conseil augmenterait d'au moins 15 % le taux de dépistage médical du MM réalisé chez les AP1D par rapport à une information orale seule.

Méthodes :

Nous avons élaboré un essai de supériorité, interventionnel, multicentrique, randomisé, en cluster sur une période de 2 ans. L'unité de randomisation était le centre hospitalier. Ainsi, au sein d'un même centre, tous les cas index (patient atteint de MM) ont reçu la même information sur le dépistage précoce (orale et écrite ou orale seule). Le critère de jugement principal était la réalisation d'un examen médical par un dermatologue ou un médecin généraliste pour la détection précoce du MM chez les AP1D dans les 12 mois suivant la visite du cas index. Les critères de jugement secondaires étaient la réalisation d'un auto-examen de la peau dans les 12 mois suivant la visite du cas index et sa fréquence, et les comportements de photo-protection.

Résultats :

Nous avons inclus dans le bras contrôle 48 cas index et 114 AP1D et dans le bras intervention 60 cas index et 166 AP1D. Un examen médical de dépistage chez les AP1D a été réalisé dans 36,1 % [28,8 ; 44,0] des cas dans le groupe intervention et 39,5 % [30,5 ; 49,1] des cas dans le groupe témoin avec un OR à 0,88 [IC95% 0,53 ; 1,47] ($p=0,63$). L'auto-examen de la peau et les comportements de photo-protection étaient souvent déclarés par les AP1D sans différence significative entre les deux groupes.

Conclusion

Notre étude a montré que la fiche conseil en plus des conseils oraux n'améliore pas l'adhésion des AP1D au dépistage du MM par rapport au conseil oral habituel. Le taux d'examen médical de la peau par un dermatologue ou médecin généraliste était faible dans les deux groupes. D'autres stratégies sont à envisager pour améliorer cette adhésion dans ce groupe à risque.

Mots-clés : étude randomisée en cluster, mélanome, prévention, intervention, examen médical de la peau, photo-protection, apparentés au premier degré

Abstract

Background:

First-degree relatives (FDRs, defined as parents, children, and siblings) of melanoma patients are at two to fivefold increased risk of developing melanoma themselves. FDRs are advised to perform self-skin examination (SSE) and annual medical total cutaneous examination (TCE) performed by a dermatologist or general practitioner, and to modify their behavior with sun protection. These advices are given orally to melanoma patients who are asked to relay the information to their FDRs.

Objective:

Our aim was to determine in a cluster randomized trial (Clinical Trials NCT02917473), the impact of providing a tip sheet to patients intended to their FDRS on early detection and sun protection behaviors in this group at risk of melanoma. Our hypothesis was that the tip sheet would increase by at least 15% the rate of TCE performed in FDRS.

Methods:

A 2-year superiority, cluster-randomized trial was conducted at 9 hospital centers. In the intervention group, dermatologists were asked to deliver to their melanoma patients the tip sheet and oral advices intended to their FDRs. In the control group, they were asked to deliver the usual oral advices alone. The primary outcome was early detection of melanoma in FDRs with a medical TCE performed within one year after the first visit of the index case. Secondary outcomes were SSE and sun protection behaviors in FDRs.

Results:

48 index cases and 114 FDRS in the control arm, 60 index cases and 166 FDRS in the intervention arm were recruited. A medical TCE was performed in 36.1% [28.8; 44.0] of FDRs in the intervention group and in 39.5% [30.5; 49.1] of FDRs in the control group (OR, 0.88; 95% CI, 0.53 to 1.47, $p = 0.63$). We did not find between-group difference in SSE and sun protection behaviors.

Conclusion:

A tip sheet added to the usual oral advices did not increase TCE among FDRs of melanoma patients. Overall, the rate of TCE among FDRs was low. Research of other strategies is needed to increase melanoma detection in this population.

Key words: cluster randomized trial, melanoma, prevention, intervention, medical skin examination, sun protection behaviors, first degree relatives

Trial Registration: ClinicalTrials.gov Identifier: NCT02917473

Article soumis pour publication

Comparison of Two Strategies to Increase Early Detection and Prevention Behavior Among First-degree Relatives of Melanoma Patients: a cluster randomized trial

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Key words: cluster randomized trial, melanoma, prevention, intervention, medical skin examination, sun protection behaviors, first degree relatives

Introduction

The incidence of cutaneous melanoma (CM) still continues to increase worldwide[1]. 15, 513 new cases per year are diagnosed in France[2] resulting in 1975 deaths /year [2]. Greater tumor thickness and delayed diagnosis are associated with higher mortality. Total cutaneous examination (TCE) performed by a dermatologist or a general practitioner (GP) and skin self-examination (SSE) are significantly associated with thinner melanomas[3][4][5]. However, prevention and early detection on a large scale in the general population are expensive and potential benefit of skin cancer screening on CM mortality has not been demonstrated[6][7]. Costs of modern treatments in advanced stages markedly increased with modern therapeutic options[8] making probable prevention programs to become cost-effective or even cost saving.

First-degree relatives (FDRs) are at greater risk of developing CM[9][10][11]. Personalized screening of at-risk subjects is recommended in many countries including France[12]. A computer simulation study carried out in the USA before the modern era of effective but costly medical treatments of advanced stages, found that a biennial consultation is cost-effective in FDRs of CM patients[13]. Therefore, patients with newly diagnosed melanoma are orally advised to inform their FDRs of the increased risk, and to transmit counselling about the usefulness of protecting their skin from sun exposure, and proceeding to SSE and consult annually a dermatologist or a GP for TCE. The best way to deliver the message of sun protection and screening in order to induce, behavioral changes from FDRs and the psychological determinants of adherence to prevention message are not fully understood[14][15][16]. The lack of written support for relatives was considered a communication barrier by 49% of dermatologists surveyed in the USA in 2012[17]. A pilot study performed in our center suggested that a tip sheet delivered to CM patients for their relatives and promoting sun protection and TCE was efficient to promote TCE in FDRs. CM patients reported a significant increase in medical TCE by their relatives (50.5% vs 87.5%, $p=0.006$), but TCE was self-reported thus subject to bias[18]. Moreover this study was observational rather than randomized.

We report a cluster-randomized trial that aims at assessing whether the delivery of a tip sheet and usual oral counselling could be efficient to incite FDRs to perform SSE, TCE and sun protection behaviors in FDRs of CM patients, as compared to usual oral counselling only.

Methods

Design

We performed a superiority, cluster randomized controlled trial using hospital centers (7 academic and 2 non academic hospitals) as randomization units to limit contamination biases.

Setting and Participants

We conducted the study in France in nine hospital centers between January 2014 and May 2019 and we enrolled participants from 13/12/2017 to 26/04/2019.

During one of the first initial management visits (initial resection or wide surgery or first follow up visit) patients with CM (index case) received information on the usefulness of early detection of CM and sun protection of their FDRs (either oral and written in the intervention group, or oral alone in the control group).

During follow-up visit, one year later, the non-opposition of CM patients was recorded. CM patients, who did not object, provided contact details for their FDRs. Questionnaires and scales were completed by the index cases to assess the actual distribution of the tip sheet to their FDRs who were then contacted by telephone. After expressing their non-opposition orally, the criteria for evaluating early detection of melanoma and sun protection were collected. In both arms, newsletter and non-opposition sheet were mailed to the FDRs along with questionnaires assessing the determinants of their behavior. FDRs were invited to complete and return the documents via a return envelope to the coordinating center. In the absence of a telephone response, FDRs were contacted by email and in the absence of a response to this email or in the absence of an email address, by post. (Figure 1)

Index cases with CM were informed of the study one year after initial diagnosis of their melanoma and were proposed to take part to the study.

Inclusion criteria of CM patients

Patients who were 18 years of age or older, speaking French, treated for stage I or II primary cutaneous CM in one of the centers participating in the study, and who were received in consultation at the time of diagnosis (less than 3 months after the excision). Patient must have at least one FDRS.

Exclusion criteria of CM patients

Patients with mucous or ocular melanoma, who have no FDRs, or who do not wish to communicate information concerning melanoma to their FDRs were excluded.

Inclusion criteria for FDRs participating in the study were to be over 18 years-old and to be first degree related (brothers and sisters, children, father and mother to an index case).

Randomization, intervention and control procedures

Hospital centers were randomly allocated to written and oral information or oral information only in a 1:1 ratio. Allocation schedule was independently performed by a statistician using a computer-generated randomization list. Randomization was stratified on the type of hospitals academic or non-academic. This was an unblinded study.

Intervention arm consisted of usual care, *i.e.* oral counselling plus a tip sheet which explained to the patients that they should inform their FDRs that they are at risk of CM and consequently should perform SSE and TCE and change their behavior regarding sun exposure by seeking shade, using hat, long sleeve clothes and sun protection creams.

The tip sheet was established prior to the beginning of the study by the medical staff and then submitted to patients with CM and some of their relatives, in two separate sessions in focus groups lasting 2 hours each, to test their comprehension and to modify some phrases, which resulted in the final version of the tip sheet.

Control arm consisted in usual care, *i.e.* to orally advise CM patients to inform their FDRs that they are at higher risk of occurrence of CM than the general population and consequently should perform SSE and TCE and change their behavior regarding sun exposure by seeking shade, using hat, long sleeve clothes and sun protection creams.

Outcomes

The primary outcome was FDRs participation in CM early detection through TCE with a dermatologist or a general practitioner performed within 1 year after the advices (written and oral or oral alone) had been delivered to the index cases. FDRs of each index case were contacted by telephone by a clinical research assistant previously trained to perform data collection. Calls were centralized in order to standardize the assessment of FDRs. To assess the reliability of TCE self-reported by the FDRs without overburdening the study too much, a random sample of 50 FDRs (25 in the control group and 25 in the intervention group) declaring to have had TCE was drawn, and their physician (dermatologist or GP) were contacted by

telephone to ensure that they actually had a TCE consultation for the early detection of melanoma on the date they reported.

Secondary outcomes were planned TCE with a dermatologist or a general practitioner, FDRs participation in CM early detection through SSE, the number of relatives who declare to have performed SSE, sun protection behaviors assessed by a questionnaire reported by FDRs.

Adherence to the intervention was assessed by questioning the FDRs on the screening and photoprotection counselling delivered in both arms.

Statistical Analysis

In our sample size calculation, we accounted for clustering at the family level rather than at the hospital level (randomization unit) as clustering was expected to be higher within families than within hospital centers. On the basis of data from our pilot study, we hypothesized a 60% rate of TCE for FDRs in the control group, an intraclass correlation coefficient at family level of 0.40. To detect a 15% increase in TCE, a sample size of 900 FDRs was needed to have a power of 90%, at a 5% two-sided significance level. We expected an average number of 4 FDRs per CM patient thus we planned to include 225 CM patients in our trial.

Baseline characteristics of index cases and FDRs were described according to the randomization group, using mean and standard deviation or median and interquartile ranges for continuous variables, depending on the distribution) and with frequencies and percentages for qualitative variables. No statistical test was performed for these variables.

Analysis of the primary outcome and secondary binary outcomes was performed with generalized estimating equations methods. We used an exchangeable correlation matrix and robust variance estimators to account for clustering at the family level. We used logistic regression models to estimate odds ratios (OR) with 95% confidence intervals.

FDRs who performed a TCE before the initial visit of their index case and FDRs, who reported a TCE but for whom the date of completion of TCE was unknown were considered not to have completed TCE in the main analysis of the primary outcome within the timeframe provided in the protocol. A post hoc sensitivity analysis was carried out by considering that these FDRs had indeed made a TCE (even if this was prior to the initial visit of the index case or of unknown date).

Intraclass correlation coefficients (ICCs) for the primary outcome were estimated by analysis of variance (ANOVA) in each group. In order to verify our hypothesis of a higher ICC at family

level than at hospital center level, ICCs were estimated at both levels. Their 95% confidence intervals were calculated using Searle's method. ICCs were estimated only from clusters of size greater than 1.

The frequency of SSE by FDRs was described by randomization group using median and interquartile ranges. No statistical test was performed.

We also described median time from initial consultation of the index case to TCE for FDRs. No statistical test was performed on this outcome which was not initially in the protocol.

Validity of TCE self-declaration was assessed on a random sample of 50 FDRs (25 in the control group and 25 in the intervention group) who reported TCE. We described the number of false positives (*i.e.* subjects who reported a TCE and for whom the physician did not confirm the TCE) and the positive predictive value.

The analysis was conducted according to the intention to treat principle. Randomized index cases were analyzed in the group to which they were allocated by randomization. Relatives were also analyzed in the randomization group in which the index case to which they were attached was allocated. The tests were performed at two-sided alpha risk of 5%. All analyses were performed with SAS version 9.4.

Ethics

Ethics review and approval was provided by the research ethics committee of CHRU Tours n° 2016-s14 and the trial was registered on ClinicalTrials.gov, NCT02917473.

Results

Among the 9 centers, 5 were allocated to the intervention group with 75 included index cases and 4 were allocated to the control group with 66 included index cases. Two index cases were excluded in the intervention group because they were opposed to the analysis of their personal data. 196 FDRs were contacted and 27 were excluded because they were not reachable or ineligible. In the control group, 5 index cases were subsequently excluded (4 opposed to the analysis of their personal data, 1 not wishing to communicate information concerning his melanoma to his relatives). In the control group 141 FDRs were contacted and 24 were excluded they were not reachable or ineligible. Finally, we included 60 index cases with 166 eligible FDRs in the intervention arm and 48 index cases with 114 eligible FDRs in the control arm (Figure 2).

Study population

Forty-eight index cases and 114 FDRs in the control arm, 60 index cases and 166 FDRs in the intervention arm were recruited in 9 hospital centers. The characteristics of FDRs at inclusion are summarized in Table 1. The characteristics of index cases at inclusion were similar in both groups and are summarized in supplementary Table 1.

Adherence to the intervention as reported by index cases

The majority of index cases declared having informing their FDRs about their melanoma (60/60 in the intervention arm and 43/48 in the control arm respectively).

In the intervention arm, 59 of 60 index cases declared having transmitted oral advice to FDRs and 34 of 48 index cases in the control group.

Forty six of 60 index cases in the intervention arm declared having transmitted a written tip sheet to FDRs and 8 of 48 in the control arm.

Remitting a tip sheet and transmission of usual oral advice at FDRs by the index case as reported by the FDRs

In the intervention group, 55 of 166 FDRs reported that a tip sheet was remitted and 4 of 114 FDRs in the control group.

Oral advice transmitted by the index case to FDRs was declared by 121 of 166 FDRs in the intervention arm and 72 of 114 FDR in the control arm.

Primary outcome

In the intervention group, 60 of 166 FDRs reported to have had a TCE by a dermatologist and / or a GP at a date subsequent to the initial consultation of the index case versus 45 of 114 FDRs in the control group. We did not find a between-group difference in the proportion of FDRs with a TCE, 36.1% in the intervention group vs. 39.5% in the control group; OR, 0.88 (95% CI, 0.53 to 1.47, $p=0.63$) (Table 2). Sensitivity analysis accounting for all the reported TCE irrespective of the date, confirmed our primary results (71/166, 42.8% in the intervention group vs. 56/114, 49.1% in the control group; OR, 0.79 (95% CI, 0.47 to 1.34, $p=0.39$). ICCs for reported TCE in the intervention and control groups were 0.009 and 0.06 at hospital center level and 0.15 and 0.12 respectively at family level, respectively.

Among the 50 FDRs (25 in the control group and 25 in the intervention group) declaring to have had TCE and having been drawn, 39 self-declaration validity was assessable and

confirmed in all cases (17 in the control group and 22 in the intervention group). Finally, for 11 FDRs, doctors could not be reached.

Secondary outcomes

Practitioner type and median time to TCE

TCE was performed mainly by dermatologists (65/70, 92.9% in the intervention group vs. 51/56, 91.1% in the control group) and rarely by GPs (4/70 versus 3/56) or by both practitioners (1/70 versus 2/56) respectively.

Median time from index case initial visit to FDR TCE was 226 (IQR, 129; 319) in the intervention arm and 250 days (IQR, 129; 362) in the control arm.

Among the 280 FDRs, 8/166 in the intervention arm made a doctor's appointment for TCE which has not yet been completed. This occurred in 1/114 in the control arm; OR 5.52 (95% CI, 0.67 to 45.33, $p = 0.39$). Moreover, 36/166 in the intervention arm versus 24/114, in the control arm planned to make an appointment; OR 1 (95% CI, 0.58 to 1.89, $p = 0.88$) (Table 2). In the 127 FDRs who had TCE with a GP or a dermatologist, 29 had a lesion removed following this consultation, 9/56 in the control arm and 20/71 in the intervention arm; OR = 2.1 (95% CI, 0.9 to 4.8, $p = 0.08$). Three melanomas was detected in the intervention arm and 1 in the control arm; OR = 1.3 (95% CI, 0.1 to 15.0, $p = 0.85$).

Self-skin examination

SSE was reported by 110 of 166 FDRs in the intervention arm versus 69/113 in the control group; OR 1.28 (95% CI, 0.75 to 2.2, $p = 0.4$). There was no difference in the frequency of performing SSE (*i.e.* more than 1/months, 1 or 2 per year, or never) between intervention and control arm.

Sun protection behaviors

Use of strict sun protection behavior was reported by 121/166 FDRs in the intervention arm and 88/114 in the control arm; OR 0.82 (95% CI, 0.46 to 1.44, $p = 0.48$). Sun protection behaviors of the participants are summarized in Table 3

Discussion

Our study was designed to be pragmatic and in the case of positive result, easily generalized in daily practice by dermatologists. In France, usual practice is to deliver oral counselling to patients with CM to inform and encourage their FDRs to perform TCE, SSE and use sun protection behaviors. We were aware from some previous studies showing that repeated messages were efficient. From our preliminary study we hypothesized that a written leaflet given in the 3 months following removal of CM patients at destination of their FDRs would be efficient enough. Our study clearly demonstrated that a one-shot message is insufficient to improve engagement of FDRs in TCE, SSE and sun protection behavior.

Primary and secondary outcomes

The main outcome was not achieved: remitting a tip sheet to patients with melanoma did not increase the number of TCE in FDRs as compared to the usual oral advice in the control group. The main strength of the study is that the main outcome was not self-declared as we verified by calling dermatologists and GPs that an appointment for TCE has really been performed. Less than 50% of FDRs in both groups actually performed TCE by a dermatologist or general practitioner in the year following removal of melanoma in their relative. SSE as declared by FDRs was performed in 66.3% in the intervention group and 61.1% in the control group, with no statistical difference. Finally, modification of sun protection behavior as declared by FDRs was also similar in both groups.

The low rate of TCE observed in both groups of FDRs are consistent with a study conducted between 2001 and 2003 in the USA[19]. They founded that 45% of first-degree family members never had a TCE and that 13.4% had not had TCE within the past 3 years. In the same study, SSE had not been performed in the past year in 28% of FDRs versus 39% in the control group and 34% in intervention group in our study. The frequency of SSE among APD1 varies according to the different studies ranging from 30,8 to 71.6%[20][19]. Our results contrast with the 3 other previous randomized studies which showed a positive impact of tailored intervention directed to FDRs as compared to usual care[21][22] [23]. The discrepancies may be related to different designs in the intervention and control groups. In France, usual care consists in oral counselling inviting FDRs to perform TCE, SSE and to protect their skin from sun, and the intervention in our study was providing patients with tip sheet dedicated to their FDRs in addition to oral counselling.

In the 3 randomized studies, all conducted in the USA, usual care comprised oral plus written advice and intervention consisted in the repetition of phone calls or emails delivered at baseline and repeated at several times to invite participants to SSE, TCE and sun protective behavior. Geller et al.[22] first carried out a randomized study in 403 FDRs of patients with newly diagnosed CM between October 1998 and December 2000. Usual care was defined as “a standard practice of suggesting that patients diagnosed with melanoma notify family members about their diagnosis and encourage the family members to be screened”. FDRs were contacted and randomized between usual care and intervention which consisted in 1) an initial motivational and goal-setting telephone intervention session delivered by the health educator; 2) computer-generated tailored print materials were sent at 1, 3, and 5 months after randomization. 3) three telephone counseling sessions with the health educator, timed to follow receipt of the mailed materials; and 4) linkages to free screening programs. Main outcomes based on self-declaration from participants were 1-having TCE by a dermatologist as declared by participants, 2- performing SSE at least once per year and 3- always or often using sun protection factor 15 or greater. TCE performed by a dermatologist before and one year after randomization increased in both groups but the frequency did not differ between usual care and intervention (28.3 and 68.3 intervention 28.8% and 67.8% usual care; OR 1.04, 95%CI 0.54-1.98). There was no difference for sunscreen use, and a significant difference in SSE as declared by the participants in the intervention group (OR 1.16, 95% CI 1.06-2.91).

In the second randomized trial conducted between February 2006 and September 2008, Manne and et al.[21], compared tailored intervention versus generic in 443 FDRs of patients with CM diagnosed within the five past years. Usual care in 218 participants included three print mailings on a monthly timeline and one telephone call focusing on SSE, TCE and sun protection. Tailored intervention in 225 participants comprised more detailed information on SSE, TCE and sun protection, and the tailored counselling call was more detailed and lasted longer (30.2 versus 11.5 minutes). Three months and nine months after the last mailing, participants were asked to fill surveys. TCE declared by the participants were confirmed in 72% with the subject's physician versus 36.1% in the intervention arm and 39.5% in the control arm, in our study. There was a significant increase in TCE in the tailored group (OR 1.94; 95%CI 1.39-2.72) and a significant increase in sun protection habits, but no statistical difference for the frequency of SSE.

In the third trial, Bowen et al. [23] 313 FDRs of patients with CM diagnosed between April 1st 1998 and October 1st 2001 were randomized to either an immediate or delayed comparison group. Intervention consisted of an access to the study web site including every 3 months emails

containing information and inviting FDRs to connect to the website. Performing SSE was declared by 14.7 and 18.3% of FDRs at baseline and 31.2 and 16.8% at 1 year follow up in the intervention group as compared with the control group ($p=0.006$), respectively. TCE was declared by 14.7 and 14.7 % at baseline and 41.7 and 10.3 % in intervention and control groups ($p=0.005$), respectively. Some sun protection behaviors such as wearing something on the head (hat, cap, scarf) or stay in available shade were significantly improved in the intervention group ($p=0.005$ and 0.008 , respectively), but applying sunscreen SPF 15+ or higher was not improved ($p=0.88$).

Apart from the design of these 3 randomized trials with positive results in the intervention groups which all comprised repeated messages dedicated to FDRs, some other points may explain the failure of our intervention. First, we were surprised by the low rate of transmission (33.1%) of the tip sheet declared by FDRs in the intervention group versus 3.5% in the control group. The rate of transmission of an advice to perform TCE as declared by melanoma patients was 63%[24], this is close to the rate of FDRs in our study who declared having been informed by the index case to perform TCE (57.7% and 63.0% in intervention and control arms, respectively). This means that the information has been effectively transmitted by the patients in nearly two third of the patients but that the tip sheet in our study does not help to improve the communication. One of the explanations of the low rate of transmission of the tip sheet can be explained by the temporality in the announcement of the diagnosis: at first, family conversations typically focus primarily on the patient, including diagnosis and the treatment and after the resolution of this acute treatment phase, conversations about family risk and prevention predominate[25]. During this second step, melanoma patients may not inform their FDRs due to the perception of low or high risk of occurrence of melanoma in their FDRs according to skin color, ability to sunburns and age[26]. This is why tailored intervention should increase the rate of information of FDRs. During this step, the paper can be lost, forgotten, or difficult to transmit because relatives and index cases do not live in the same city for example. Thus, the paper support may not be the most suitable support. In addition, FDRs may go directly to the internet for information and find the tip sheet of little use. Indeed, in our study, FDRs frequently declared having sought information on internet in 72.5% and 64.3 % in intervention arm and control arm, respectively. Moreover, the information on skin cancers, sun protection behaviors and familial risk of cancers has been widely diffused in the media in France with a skin cancer day conducted every year, so that many patients and their family are now better informed as compared to the years 2000.

Finally, knowing the risks of a skin cancer (or other cancers) does not imply engagement in screening program and reduction or avoidance of risk factors due to addiction to known carcinogens (*e.g.* tobacco or sun exposure) or due to fatalism[27]

Limitations

The main limitation is the lack of power. We planned to include 900 FDRs, and finally we included 279 FDRS. Indeed, we overestimated the expected number of FDRs: we estimated the number of FDRs by CM patient to be 4, while patients reported only 2.6 on average which is the same as reported by Manne et al.[21]. Second, we can think that the study induced a bias: the strengthening of oral advice for patients and their relatives in the control arm. In "real life", oral advice may be very quick or forgotten and in this case, the delivery of a tip sheet might be useful in more patients. In a qualitative study, at-risk melanoma family member's stated that communications from the doctors was absent or inconsistent and the health system restricted communication[28]. Susan A. Oliveria and al[29] found that between 82.3% and 84.2% of dermatologists reported that they often or always communicate risk to patients with melanoma about their first-degree relatives. However, only 45.1% to 47.3% of dermatologists routinely offered to screen first- degree family members who live nearby. Absence of standardized guidelines or lack of written material are identified like moderate barriers to melanoma communication by dermatologists. So written material can be sometimes useful.

In summary, the message of sun protection and individual screening of relatives was retained by patients, and implemented by their relatives both in the centers which provided a tip sheet in addition to oral advice, and in the centers which only gave oral advice. It is concluded that the message delivered in this study, whether oral or oral and written, is delivered by patients to their families but that the effective performance of a skin examination by a doctor is similar in the 2 groups and remained weak. However, the study may have induced a bias: the reinforcement of oral advice for patients and their relatives in centers which did not provide a written form. In addition, in "real life", it is likely that the oral advice may be forgotten or very quick, and that then the delivery of a tip sheet might be useful in a greater number patient. Finally, improving sun protection and screening practices probably requires more intensive personalized and repeated interventions.

Tables and Figures

Figure 1. Timeline

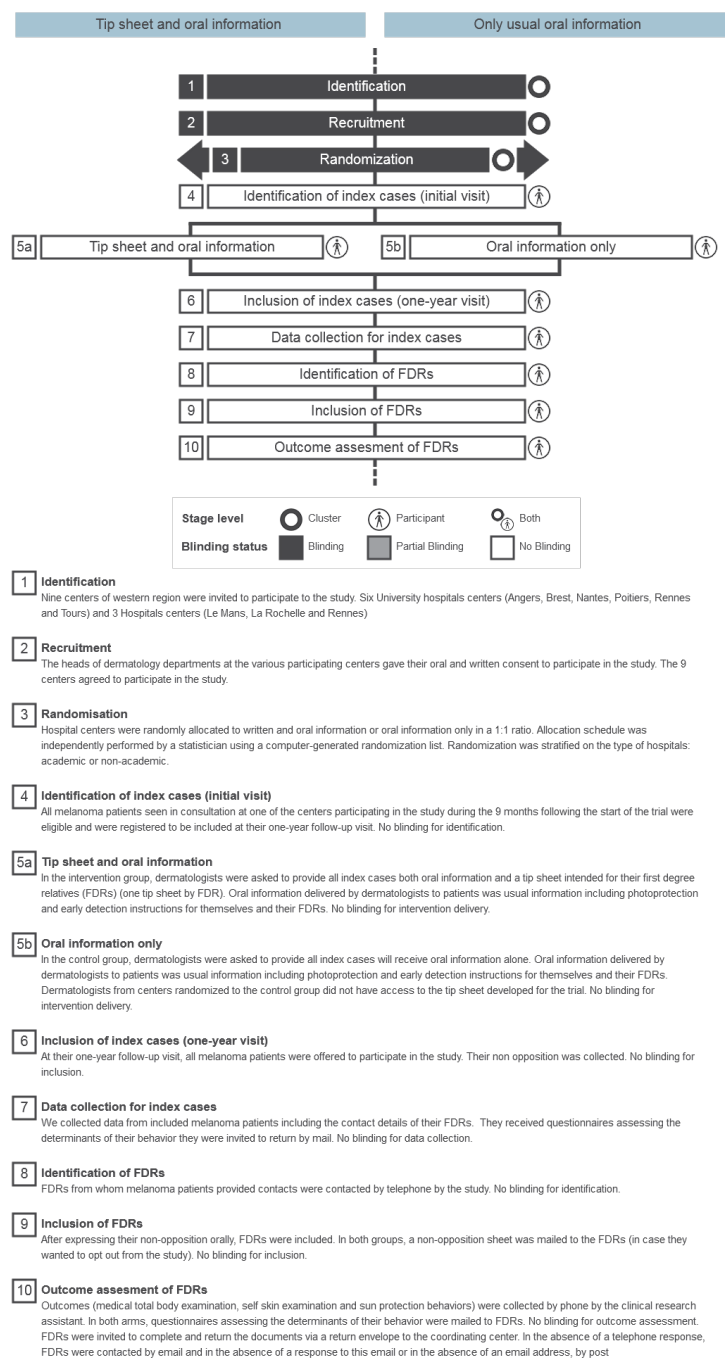
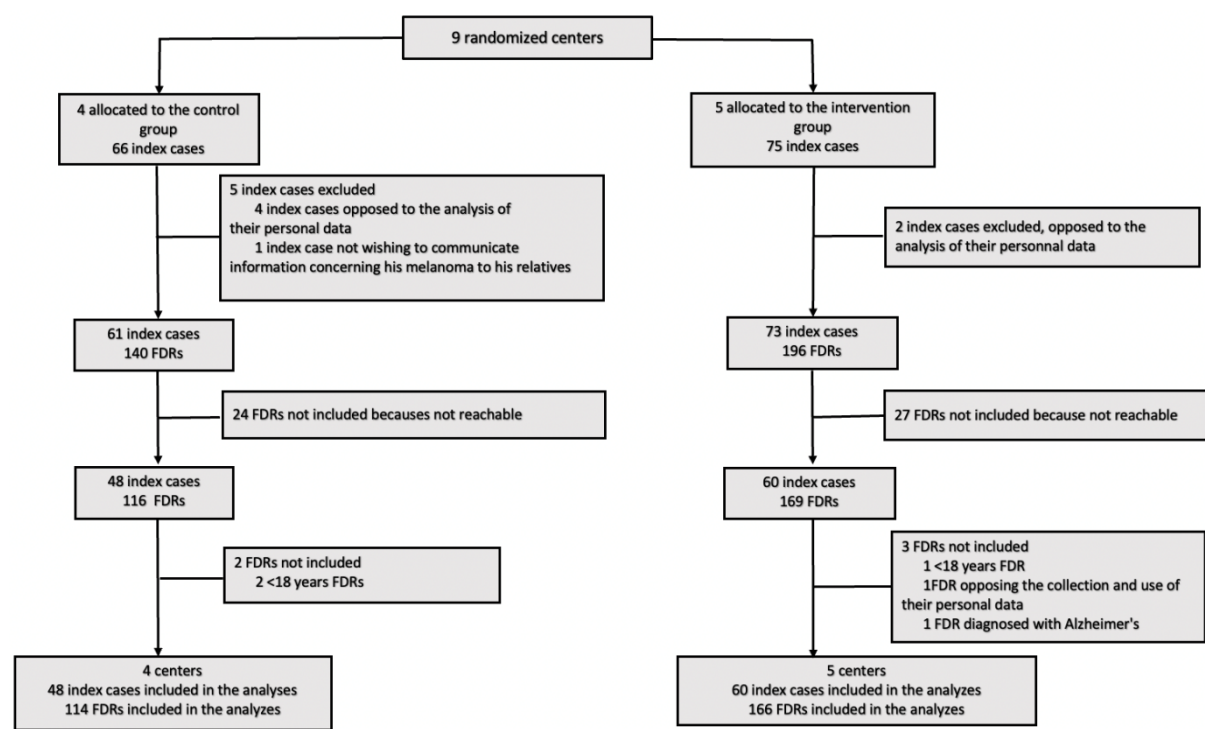


Figure 2. Flow-chart



Supplementary TABLE 1. Index cases socio-demographic characteristics and CM risk factors at inclusion

	Intervention arm Written and oral information n = 60	Control arm Oral information alone n = 48
Age, n _i =60 n _c =48	63 (15)	61 (15)
Men, n _i =60 n _c =48	31 (51.7)	23 (47.9)
Breslow thickness n _i =60 n _c = 48	1.3 (0.4 ; 2.7)	2.1(1.1 ; 3.4)
Fitzpatrick skin type		
I	12 (21.8)	6 (12.5)
II	20 (36.4)	25 (52.1)
III	21 (38.2)	17 (35.4)
IV	2 (3.6)	0 (0.0)
Number of nevus > 50, n _i =56 n _c =48	15 (26.8)	13 (27.1)
Histological type, n _i =60 n _c =48 n _i =60		
SSM ¹	45 (75.0)	30 (62.5)
NM ²	7 (11.7)	7 (14.6)
ALM ³	4 (6.7)	2 (4.2)
Other	4 (6.7)	9 (18.8)
Ulceration n _i =60 n _c =48	15 (25.0)	16 (33.3)
History of cutaneous melanoma n _i =60 n _c =48	3 (5.0)	4 (8.3)
Number of cutaneous melanoma, n _i =3 n _c =4	1 (1 ; 1)	1 (1 ; 2)
History of another cancer n _i =60 n _c =48	6 (10.0)	4 (8.3)
Skin cancer*, n _i =6 n _c =4	3 (50.0)	1 (25.0)
Other type of cancer*, n _i =6 n _c =4	4 (66.7)	4 (100.0)
Family history of melanoma n _i =60 n _c =47	11 (18.3)	9 (19.1)
Number of people involved n _i =11 n _c =9	1 (1 ; 1)	1 (1. 1)
Family history of cancer n _i =60 n _c =46	24 (40.0)	21 (45.7)

Data are n (%), mean (SD) or median (interquartile range).

*a patient could have several history of cancer

¹SSM Superficial Spreading Melanoma

²NLM Nodular Lentiginous Melanoma

³ALM Acral Lentiginous Melanoma

TABLE 1. First degree relatives socio-demographic characteristics, center characteristics and MM risk factors at inclusion

N (%) or mean (standard deviation) or Median [Q1 ; Q3]	Intervention arm Written and oral information n = 166	Control arm Oral information alone n = 114
Center characteristics		
Hospital center	2 (40.0)	1 (25.0)
University hospital center	3 (60.0)	3 (75.0)
First degree relatives characteristics		
Age, n _i =165, n _c =114	52 (17)	50 (18)
Men n _i =166 n _c =114	75 (45.2)	45 (39.5)
Level of education, n _i =166 n _c =114		
Secondary school	24 (14.5)	15 (13.2)
Certificate of professional competence / Professional study certificate	34 (20.5)	26 (22.8)
High school diploma	43 (25.9)	38 (33.3)
Bachelor's degree	32 (19.3)	16 (14.0)
Master's degree	32 (19.3)	18 (15.8)
Other	1 (0.6)	1 (0.9)
Occupational status n _i =166 n _c =114		
Full-time professional	95 (57.2)	59 (51.8)
Part-time professional	10 (6.0)	7 (6.1)
No activity	1 (0.6)	0 (0.0)
Work time accident/occupational disease	2 (1.2)	0 (0.0)
Student	6 (3.6)	7 (6.1)
Disability	1 (0.6)	0 (0.0)
Unemployment	0 (0.0)	3 (2.6)
Retired	49 (29.5)	36 (31.6)
Other	2 (1.2)	2 (1.8)
Business, n _i =165 n _c =113		
Farmer	2 (1.2)	0 (0.0)
Artisan, trader, head of enterprise	10 (6.1)	6 (5.3)
Executive, higher intellectual profession	25 (15.2)	17 (15.0)
Intermediate occupation	11 (6.7)	2 (1.8)
Employed	58 (35.2)	38 (33.6)
Worker	1 (0.6)	3 (2.7)
Other	58 (35.2)	47 (41.6)
Family situation, n _i =165 n _c =114		
Married	113 (68.5)	76 (66.7)
Single	36 (21.8)	19 (16.7)
Widow(er)	6 (3.6)	5 (4.4)
Separated / divorced	10 (6.1)	14 (12.3)
FDRs with children n _i =165 n _c =114	117 (70.9)	80 (70.2)
Number of children, n _i =117 n _c =80	2 (2 ; 3)	2 (2 ; 3)
History of melanoma, n _i =161 n _c =112	6 (3.7)	3 (2.6)
History of another cancer n _i =163 n _c =113	12 (7.4)	10 (8.8)
Skin cancer*, n _i =12 n _c =10	5 (41.7)	6 (60.0)
Other type of cancer*, n _i =12 n _c =10	7 (58.3)	5 (50.0)

Data are n (%), mean (SD) or median (interquartile range).

* a patient could have several history of cancer

TABLE 2. TCE actually carried out by a dermatologist and / or a general practitioner with examination for the early detection of MM according to the randomization group - making an appointment / planning to take an appointment for an examination early detection

	Intervention arm Written and oral information n = 166	Control arm Oral information n = 114	OR	p value
TCE performed strictly within the period of the study*	n = 60 36.1%	n = 45 39.5%	0,9 [0.5;1.5]	0.63
Sensitivity analysis - TCE performed including TCE performed just before the inclusion period, or with missing date of appointment.	n = 71 42.8%	n=56 49.1%	0,8 [0,5;1;3]	0.39
TCE planned with an appointment but which has not yet been completed	n = 8 4.8%	n = 1 0.9%	5.5 [0.7;45.3]	0.11
TCE planned with no appointment yet	n = 36 21.8%	n = 24 21.1%	1.1 [0.6;1.9]	0.88

* In this analysis, patients who had a screening exam on an unknown date or before the initial visit were considered as "failure".

TABLE 3. Sun protection behaviors of FDRs

	Intervention arm Written and oral information n = 166	Control arm Oral infor- mation n = 114	OR	p-value
Use of sun protection	n = 121 72.9%	n = 88 77.2%	0.8 [0.5;1.4]	0.48
Avoidance of sun exposure	n = 39 23.5%	n = 22 19.3%	1.4 [0.7;2.7]	0.40
Wearing protective clothes	n = 70 57.9%	n = 38 43.2%	1.5 [0.9;3.3]	0.13
Use of high index sunscreen	n = 105 63.3%	n = 70 61.4%	1.1 [0.6;1.8]	0.73

Liste des abréviations

AP1D Apparentés au premier degré

CM Cutaneous Melanoma

FDRs First-degree Relatives

GEE Generalized Estimating Equations

GP General Practitioner

ICC Intra-Center Correlation

MM Mélanome cutané Malin

OR Odds Ratio

SSE Self-Skin Examination

TCE Total Cutaneous Examination

Références

1. GLOBOCAN 2020. Available from: <http://gco.iar.fr>.
2. e-cancer. Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018. Volume 1 – Tumeurs solides. :372.
3. Swetter SM, Pollitt RA, Johnson TM et al. Behavioral determinants of successful early melanoma detection. *Cancer*. 2012;118:3725–34.
4. Kovalyshyn I, Dusza SW, Siamas K, et al. The Impact of Physician Screening on Melanoma Detection. *Arch Dermatol*. 2011;147:1269–75.
5. Dessinioti C, Geller AC, Stergiopoulou A, et al. Association of Skin Examination Behaviors and Thinner Nodular vs Superficial Spreading Melanoma at Diagnosis. *JAMA Dermatol*. 2018;154:544–53.
6. Wernli KJ, Henrikson NB, Morrison CC, et al. Screening for Skin Cancer in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2016;316:436–47.
7. Johansson M, Brodersen J, Gøtzsche PC, et al. Screening for reducing morbidity and mortality in malignant melanoma. *Cochrane Database Syst Rev*. 2019;2019:CD012352.
8. Buja A, Sartor G, Scioni M, et al. Estimation of Direct Melanoma-related Costs by Disease Stage and by Phase of Diagnosis and Treatment According to Clinical Guidelines. *Acta Derm Venerol*. 2018;98:218–24.
9. Balch CM, Soong SJ, Shaw HM, et al. An analysis of prognostic factors in 8500 patients with cutaneous melanoma. Cutaneous melanoma. *Philadelphia: JB Lippincott*. 1992;163–87.
10. Ford D, Bliss JM, Swerdlow, et al. Risk of cutaneous melanoma associated with a family history of the disease. The Interventional Melanoma Analysis Group (IMAGE). *Int J Cancer*. 1995;62:377–381.
11. Rhodes AR, Weinstock MA, Fitzpatrick TB, et al. Risk factors for cutaneous melanoma. A practical method of recognizing predisposed individuals. *JAMA*. 1987;258:3146–54.
12. https://www.has-sante.fr/upload/docs/application/pdf/201203/ald_30_guide_melanome_web.pdf
13. Losina E, Walensky RP, Geller A, et al. Visual screening for malignant melanoma: a cost-effectiveness analysis. *Arch Dermatol*. 2007; 143:21–8
14. Coroiu A, Moran C, Bergeron C, et al. Operationalization of skin self-examination in randomized controlled trials with individuals at increased risk for melanoma: A systematic review. *Patient Education and Counseling*. 2020;103:1013–26.
15. Bowen DJ, Hay JL, Mayer J, Kuniyuki A, Meischke H, Harris J, et al. Predictors of recruited melanoma families into a behavioral intervention project. *Contemp Clin Trials*. 2012;33:85–92.
16. Bowen DJ, Albrecht T, Hay J, et al. Communication Among Melanoma Family Members. *J Health Commun*. 2017;22:198–204.
17. Oliveria SA, Heneghan MK, Halpern AC, et al. Communication About Family Members' Risk of Melanoma: Self-reported Practices of Dermatologists in the United States. *Arch Dermatol*. 2012;148:621–7.

18. Berton M, Perrinaud A, Samimi M, et al. Utilité d'une fiche de conseils pour la photoprotection et le dépistage des patients et de leur famille après un diagnostic de mélanome. *Ann Dermatol Veneréol*. 2013 ; 140 : S407-408.
19. Manne S, Fasanella N, Connors J, et al. Sun protection and skin surveillance practices among relatives of patients with malignant melanoma: prevalence and predictors. *Prev Med* . 2004;39:36–47.
20. Solak SS, Yondem H, Cicin I. Evaluating sun protection behaviors and skin self-examination practices among the family members of melanoma patients in Turkey: A cross-sectional survey study. *Dermatol Ther*. 2020;33:e14268.
21. Manne S, Jacobsen PB, Ming ME, et al. Tailored versus generic interventions for skin cancer risk reduction for family members of melanoma patients. *Health Psychology*. 2010;29:583–93.
22. Geller AC, Emmons KM, Brooks DR, et al. A randomized trial to improve early detection and prevention practices among siblings of melanoma patients. *Cancer*. 2006;107:806–14.
23. Bowen DJ, Hay J, Meischke H, et al. Randomized trial of a web-based survivor intervention on melanoma prevention behaviors of first-degree relatives. *Cancer Causes Control*. 2019;30:225–33.
24. Rodríguez VM, Berwick M, Hay JL. Communication about melanoma and risk reduction after melanoma diagnosis. *Psycho-Oncology*. 2017;26:2142–8.
25. Hay J, Shuk E, Brady MS, et al. Family Communication After Melanoma Diagnosis. *Arch Dermatol*. 2008;144:553–4.
26. Oliveria SA, Shuk E, Hay JL, et al. Melanoma survivors: health behaviors, surveillance, psychosocial factors, and family concerns. *Psycho-Oncology*. 2013;22:106–16.
27. Loescher LJ, Crist JD, Siaki LACL. Perceived Intra-Family Melanoma Risk Communication. *Cancer Nurs*. 2009;32:203–10.
28. Loescher LJ, Crist JD, Cranmer L, et al. Melanoma high-risk families' perceived health care provider risk communication. *J Canc Educ*. 2009;24:301–7.
29. Oliveria SA, Heneghan MK, Halpern AC, Hay JL, Geller AC. Communication About Family Members' Risk of Melanoma: Self-reported Practices of Dermatologists in the United States. *Arch Dermatol*. 2012 ; 148:621–7.

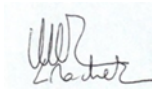
Conclusion générale

Les messages personnalisés ont le potentiel de concentrer les efforts de prévention sur les personnes les plus à risques, augmentant ainsi l'efficacité des interventions de la prévention du cancer. Des études antérieures ont montré un impact positif d'une intervention pour la prévention du mélanome chez les AP1D avec des messages répétés et personnalisés.

Globalement, dans notre étude, le message de photo-protection et de dépistage individuel des apparentés était retenu par les patients, et mis en œuvre par leurs apparentés aussi bien dans les centres qui remettaient une fiche conseil en plus des conseils oraux, que dans les centres qui délivraient seulement un conseil oral. On en conclut que le message délivré dans cette étude, qu'il soit oral ou bien oral et écrit, est délivré par les patients à leur famille mais que la réalisation effective d'un examen cutané par un médecin est similaire dans les 2 groupes et est restée faible.

On peut penser que l'étude a induit un biais (effet Hawthorne) : le renforcement du conseil oral à destination des patients et de leurs apparentés dans les centres qui ne remettaient pas de fiche. De plus dans « la vraie vie », il est probable que le conseil oral soit oublié ou allégé, et qu'alors, la remise d'une fiche puisse trouver une utilité chez certains patients. L'amélioration des pratiques de photo-protection et de dépistage dans ces groupes à risque nécessite probablement des interventions personnalisées plus intensives comme cela a été démontré récemment dans 3 essais randomisés.

Vu le directeur de thèse :

A small, square, light blue stamp containing a handwritten signature in black ink. The signature appears to be 'J. L. Lachet'.

Vu le doyen

De la Faculté de Médecine de Tours

Tours, le :