The Prognostic Value of \textit{BRAF} Mutation in Colorectal Cancer and Melanoma: A Systematic Review and Meta-Analysis

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Abstract

\textbf{Background:} Mutation of \textit{BRAF} is a predominant event in cancers with poor prognosis such as melanoma and colorectal cancer. \textit{BRAF} mutation leads to a constitutive activation of mitogen activated protein kinase pathway which is essential for cell proliferation and tumor progression. Despite tremendous efforts made to target \textit{BRAF} for cancer treatment, the correlation between \textit{BRAF} mutation and patient survival is still a matter of controversy.

\textbf{Methods/Principal Findings:} Clinical studies on the correlation between \textit{BRAF} mutation and patient survival were retrieved from MEDLINE and EMBASE databases between June 2002 and December 2011. One hundred twenty relevant full text studies were categorized based on study design and cancer type. Publication bias was evaluated for each category and pooled hazard ratio (HR) with 95\% confidence interval (CI) was calculated using random or fixed effect meta-analysis based on the percentage of heterogeneity. Twenty six studies on colorectal cancer (11,773 patients) and four studies on melanoma (674 patients) were included in our final meta-analysis. The average prevalence of \textit{BRAF} mutation was 9.6\% in colorectal cancer, and 47.8\% in melanoma reports. We found that \textit{BRAF} mutation increases the risk of mortality in colorectal cancer patients for more than two times; HR = 2.25 (95\% CI, 1.82–2.83). In addition, we revealed that \textit{BRAF} mutation also increases the risk of mortality in melanoma patients by 1.7 times (95\% CI, 1.37–2.12).

\textbf{Conclusions:} We revealed that \textit{BRAF} mutation is an absolute risk factor for patient survival in colorectal cancer and melanoma.

Introduction

The mitogen activated protein kinase (MAPK) pathway is one of the most crucial pathways in regulation of cancer cell proliferation and survival [1]. Constitutive activation of the MAPK pathway in cancers has been frequently observed in various malignancies which is usually due to activating mutations in upstream factors such as RAS and RAF [2]. Accordingly, mutations in \textit{BRAF} are reported in up to 70\% of cancer cell lines [3] and they are highly prevalent in most common cancers with poor prognosis such as malignant melanoma [3,4]. Mutations in \textit{BRAF} have been reported in up to 60\% of melanoma cases, between 40 to 70\% of thyroid carcinomas, and up to 18\% of colorectal cancers [3,5].

So far, over 50 distinct mutations have been identified in the \textit{BRAF} gene, which are present either in the glycine-rich P-loop of the N lobe or the activating segment in the exon 15 region [6]. Most of these mutations increase \textit{BRAF} activity by 1.5 to 700 folds depending on the type of the mutation [6]. Of all \textit{BRAF} activating mutations, a transitional mutation in nucleotide 1799 (T-A), also known as \textit{BRAF}-V600E, is the most common change. In fact, this single mutation dramatically increases \textit{BRAF} activity and accounts for more than 80\% of all reported \textit{BRAF} mutations in tumors [3,6]. This point mutation results in a valine to glutamic acid substitution that exposes the active site (normally sealed in a hydrophobic pouch) and implicates the constitutive activation of \textit{BRAF}. As a result, malignant cells with \textit{V600E} mutation proliferate in a growth factor-independent manner in culture as well as in tumors in animal models [7]. In addition, it has been demonstrated that \textit{BRAF} mutation is highly involved in main steps of cancer development and progression [8]. Together, these reports nominate the \textit{BRAF}-V600E mutation as a very promising therapeutic target in \textit{BRAF} mutated cancers. So far, \textit{BRAF} inhibitor PLX4032 is one of the only few promising treatments for malignant melanoma approved by the US Food and Drug Administration.

Although there are multiple reports on the correlation of \textit{BRAF} mutation with a variety of cancer progression steps, the correlation between \textit{BRAF} mutation and cancer patient survival is still a matter of controversy in different reports [9–15]. In this study, we...
used systematic review and meta-analysis as the most reliable approach to investigate whether BRAF-V600E mutation is associated with patient outcome. A pool of studies published between 2002 and 2011 on the association between BRAF-V600E mutation and patient survival in colorectal cancer, malignant melanoma and papillary thyroid carcinoma were reviewed and analyzed for this study. We found that BRAF mutation increases the risk of mortality in colorectal cancer patients by more than two-fold. In addition, we revealed that BRAF-V600E mutation also increases the risk of mortality in melanoma patients by 1.7 times, while its effect on papillary thyroid carcinoma still requires further investigation.

Methods

Search Strategy and Selection Criteria
We conducted a comprehensive search of medical literature on studies evaluating the effect of BRAF-V600E mutation on cancer patient survival. We searched MEDLINE and EMBASE using the terms “BRAF”, “BRAF mutation”, “BRAF V600E”, “cancer”, “patient survival”, “colorectal cancer”, “melanoma”, and “papillary thyroid carcinoma” in different combinations from June 2002 to December 2011. We initially narrowed our search based on research title followed by abstract and finally full texts were reviewed if they were categorized as relevant reports. We did not restrict the language in our research. All of the references from review papers and original reports were checked for further relevant studies in the systematic review.

Studies were excluded if contained no clinicopathologic data, survival analysis, or no comparison between wild type and mutant BRAF. In addition, studies which only reported a progression free survival as well as in vitro and animal reports were also excluded. For more information in detail please refer to PRISMA checklist (Table S1).

Data Extraction and Study Assessment
Two independent reviewers (GSA and LT) reviewed each full text report for eligibility and extracted required data. For each study the data on the number of patients in each group, mean survival time, hazard ratio and mean progression free survival time for randomized controlled trials (RCT), cancer type and study design were obtained and a consensus was achieved on all items. In the cases of incomplete required information, authors were contacted for additional information which was added as best as possible. Duplication of data was avoided by matching the author’s name and the name of the research centers.

Statistical Analysis
We started summarizing the effect of BRAF-V600E mutation on patient survival separately based on study design RCT versus cohort and cancer type. We evaluated the publication bias using funnel plot analysis. We also assessed the heterogeneity of the studies using chi-square test of heterogeneity and I² measure of inconsistency. Significant heterogeneity was defined as a Chi-square test P value of <0.10 or as an I² measure >50%. Estimated hazard ratio (HR) was calculated using odds ratio and confidence interval in studies where HR was not available. In the absence of heterogeneity HRs and CIs were calculated according to a fixed model [16] which assumes that results across studies differ only by sampling error. In those studies where only the survival curve was available with no other detailed information, survival rates were extracted over multiple time periods in order to reconstruct HR and its variance with the assumption that patient censor rate was constant during study follow-up. This method has been described previously by Parmar et al. [17] to extract summary statistics for meta-analysis. A HR > 1 was considered as a risk factor for worse survival in patient with positive BRAF mutation. In the end we used a log hazard ratio in the pooled data for the final analysis using R software [2011, The R Foundation for Statistical Computing]. The impact of BRAF mutation on patient survival was considered statistically significant if 95% confidence interval for individual or overall log HR did not overlap zero.

Results

Number of Studies
A total of 565 studies were retrieved from our electronic search. Of these, 120 abstracts were considered relevant and full texts were reviewed in detail. By the end of the review 26 studies on colorectal cancer (5 RCTs and 21 cohorts; 11,773 patients) met our inclusion criteria for meta-analysis. In addition, four studies on melanoma (1 RCT and 3 cohorts; 674 patients) including one study published at the time of statistical analysis [18] were incorporated in our final meta-analysis (Figure 1). Please also refer to complete PRISMA flow diagram (Figure S1) for more information. We were able to extract the overall survival information from two studies on papillary thyroid carcinoma [19,20]. However, we did not perform meta-analysis on papillary thyroid carcinoma subject due to the small number of studies (Table 1). The funnel plot for colorectal cancer but not for melanoma studies showed a publication bias in our collected data.

Impact of BRAF-V600E Mutation on Colorectal Cancer Patient Survival
In our pooled data for colorectal cancer only one paper reported a protective HR (less than one) for BRAF mutation. Accordingly, Zlobec et al [13] observed a protective HR of 0.53 (0.3–1.3) for left side colon cancer. However, they reported a higher HR of 2.82 (1.5–5.5) for BRAF mutation as a risk factor for right side colon cancer in the same report. We considered these two analyses as separate reports in our final analysis. The pooled log HR of BRAF mutation effect on patient survival in colorectal cancer for cohort and RCT studies were 0.98 (0.60–1.16) and 0.61 (0.28–0.94), respectively. The final log HR for all studies on colorectal cancer was 0.61 (0.60–1.03) which corresponds to a HR of 2.24 (1.82–2.93, 95% CI). The heterogeneity of data on colorectal cancer was significant (P<0.0001) and I² estimate of variation between analyzed studies was 74.3% (Figure 2).

Impact of BRAF-V600E Mutation on Melanoma Patient Survival
One RCT study [21] compared BRAF mutation in patients’ serum level with tumor samples but had no data on wild type BRAF status. Two other RCTs evaluated progression-free survival (PFS) with either no overall survival information [22] and non-significant PFS or no overall survival data on wild type BRAF group [23]. One cohort study used age <55 years as a surrogate marker for BRAF mutation while others either reported PFS or non-significant difference with no detailed information or survival curve graphs (Table 1). Pooled log HR for BRAF mutation effect on patient survival in melanoma for cohort studies was 0.57 (0.35–0.80) and the final pooled log HR including one RCT was 0.53 (0.32–0.75) corresponding to a HR of 1.70 (1.37–2.12, 95% CI). The heterogeneity of the data was not significant (P=0.467) and I² estimate of variation between analyzed studies was 0.0% (Figure 3).
Impact of \textit{BRAF-V600e} Mutation on Papillary Thyroid Carcinoma Patient Survival

One study [24] reported no death in wild type \textit{BRAF} group after almost 221 months of follow up. Another study [20] reported just one death in wild-type \textit{BRAF} group after 20 years of follow up with odds ratio of 14.63 (1.28–167.29) for mutant \textit{BRAF}. The study by Musholt \textit{et al} [19] reported no difference in overall survival (HR = 1.04), while two other reports [10,25] showed no difference in disease-free survival between mutant and wild-type \textit{BRAF} patients. However, another study by Abubaker \textit{et al} [26] found \textit{BRAF} mutation as a risk factor for disease free survival and Costa \textit{et al} [27] reported that \textit{BRAF} mutation would affect patient survival only if it is considered in combination with other mutations but not alone. In addition, Wang \textit{et al} [28] reported that patients with synchronous bilateral papillary thyroid carcinoma, which harbor more \textit{BRAF} mutation, have worse survival compared with those who have unilateral papillary thyroid carcinoma (Table 2).

\textbf{Discussion}

\textit{BRAF} mutation has become an important research topic in cancer biology since the original observation by Davies \textit{et al} [3] in 2002. They revealed that high frequency of \textit{BRAF} mutation is a common phenomenon in multiple types of cancers. Since then, numerous studies investigated the role of \textit{BRAF} mutation in cancer development and progression. In mechanistic point of view, \textit{BRAF-V600E} mutation, as the most prevalent \textit{BRAF} mutation, changes the inactive conformation of \textit{BRAF} kinase to a very active state [6]. This simple point mutation leads to a constitutive activation of whole MAPK pathway, which mediates the cell surface growth signals to transcriptional activity of cell cycle regulatory genes. The key regulatory role of \textit{BRAF} mutation in MAPK activation especially in melanoma generated a tremendous research effort to block this signaling pathway for cancer treatment. The usage of most available multi-kinase inhibitor at that time, sorafenib, was the first step toward targeted \textit{BRAF} inhibition. Despite the first promising results in cell culture and animal studies, sorafenib was found to be unsuccessful in melanoma patients treatment even among those harboring mutant \textit{BRAF} [29,30]. A number of other small molecule inhibitors have been tested for targeted \textit{BRAF} inhibition; however, so far only PLX4032 and GSK2118436 have successfully been used in clinical stages [31,32]. Taking everything into account, the main goal in cancer treatment is to increase patient survival, while the idea of whether \textit{BRAF} mutation per se actually affects patient survival has been a matter of debate. In this study, by conducting meta-analysis on data reported in 30 independent studies, we evaluated the effect of \textit{BRAF-V600E} mutation on patient survival in colorectal cancer and melanoma. We also reviewed another 10 independent studies on papillary thyroid carcinoma in which \textit{BRAF} mutation is prevalent.

In a population of 11,773 patients from 26 independent studies, we found that the risk of mortality in colorectal cancer patients harboring \textit{BRAF-V600E} mutation is more than two times higher than those with wild-type \textit{BRAF}. We also demonstrated that melanoma patients with \textit{BRAF} mutation have a 1.7 times higher risk of mortality when compared with their counterparts without \textit{BRAF} mutation in a population of 674 patients from the pooled result of 4 studies. In fact, this significant hazard ratio for \textit{BRAF} mutation in our study can indirectly explain the previously reported promising improvement of melanoma patient survival harboring \textit{BRAF} mutation after selective \textit{BRAF} inhibitor treatments [32–34]. However, short period of symptom free survival and resistance to drug therapy are new emerging problems in \textit{BRAF} specific inhibitor treatments in melanoma patients. Although the preliminary results for \textit{BRAF} inhibitor treatments...
| Country          | Study design | Number of patients | Overall survival | Hazard ratio |
|------------------|--------------|--------------------|------------------|--------------|
|                  |              | Overall | BRAF mutant | BRAF WT | Overall | BRAF mutant | BRAF WT | Overall | BRAF mutant | BRAF WT | Overall | BRAF mutant | BRAF WT | Overall | BRAF mutant | BRAF WT |
| COLORECTAL CANCER|              |         |             |          |          |          |          |          |          |          |         |          |          |          |          |          |
| Barault L [11]   | France       | Cohort  | 582        | 506      | 76       | (13.1%)  | 2.61     | (1.35–2.92) | 1.2     | (0.55–2.61) |
| De Roock W [55]  | Belgium      | Cohort  | 886        | 725      | 36       | (4.7%)   | 54       | (1.85–4.65) | 2.93    | (0.87–3.57) |
| Farina-Sarasqueta A [45] | Netherland | Cohort  | 258        | 165      | 38       | (18.7)   | 54       | (1.30–2.18) | 2.22    | (0.87–3.57) |
| Ferracin M [56]  | Italy        | Cohort  | 93         | 72       | 7        | (8.9%)   | 54       | (1.85–4.65) | 2.3     | (0.87–3.57) |
| French AJ [12]   | USA          | Cohort  | 533        | 413      | 77       | (15.7%)  | 68       | (1.08–1.8)  | 1.2     | (0.8–1.8)   |
| Laurent-Puig P [57] | France       | Cohort  | 173        | 110      | 5        | (4.3%)   | 74       | (1.08–1.7)  | 2.22    | (0.87–3.57) |
| Liao W [58]      | China        | Cohort  | 61         | 58       | 9        | (9.0%)   | 11       | (1.08–1.8)  | 2.016   | (0.61–6.58) |
| Liou JM [59]     | Taiwan       | Cohort  | 314        | 302      | 12       | (3.8%)   | 54       | (1.85–4.65) | 3.9     | (1.31–11.66)|
| Loupakis F [48]  | Italy        | Cohort  | 138        | 74       | 13       | (14.9%)  | 41       | (1.48–3.44) | 1.96    | (0.8–3.44)  |
| Maestro ML [60]  | Spain        | Cohort  | 351        | 312      | 12       | (7.7%)   | 41       | (1.48–3.44) | 1.62    | (0.50–5.21) |
| Maughan TS [61]  | UK           | RCT     | 1630       | 1189     | 102      | (7.9%)   | 88       | (2.04–8.27) | 1.82    | (1.36–2.43) |
| Ogino S [62]     | USA          | Cohort  | 649        | 526      | 105      | (16.6%)  | 54       | (2.04–8.27) | 1.97    | (1.13–3.42) |
| Park JH [63]     | Korea        | Cohort  | 75         | 66       | 5        | (7%)     | 2.46     | (1.24–4.84) | 3.06    | (1.24–4.84) |
| Price TJ [49]    | Australia    | Cohort  | 471        | 282      | 33       | (10.5%)  | 20.8     | (1.74–20.31)| 2.04    | (1.20–2.87) |
| Richman SD [34]  | UK           | RCT     | 2135       | 638      | 54       | (7.8%)   | 103      | (1.24–4.84) | 1.82    | (1.36–2.43) |
| Roth AD [41]     | Switzerland  | RCT     | 1404       | 1204     | 103      | (7.9%)   | 13.5     | (1.31–4.72) | 1.59    | (0.65–3.91) |
| Samowitz WS [64] | USA          | Cohort  | 763        | 723      | 40       | (5.2%)   | 13.5     | (1.31–4.72) | 4.23    | (1.65–10.84)|
| Saridaki Z [65]  | Greece       | Cohort  | 112        | 104      | 8        | (7.1%)   | 13.5     | (1.31–4.72) | 3.6     | (1.7–7.5)   |
| Shaukat A [66]   | USA          | Cohort  | 194        | 129      | 36       | (21.8%)  | 24.5     | (1.28–1.47) | 1.95    | (1.18–3.20) |
| Souglakos J [67] | Greece/USA   | Cohort  | 168        | 155      | 13       | (7.7%)   | 40.5     | (2.48–4.84) | 4.5     | (2.48–4.84) |
| Tie J [68]       | Australia    | Cohort  | 525        | 473      | 52       | (9.9%)   | 13.5     | (1.31–4.72) | 2.48    | (1.31–4.72) |
| Tol J [69]       | Netherland   | RCT     | 559        | 473      | 45       | (8.7%)   | 24.5     | (1.31–4.72) | 3.2     | (1.31–4.72) |
| Tran B [70]      | Australia/USA| Cohort  | 524        | 467      | 57       | (10.9%)  | 34.7     | (1.11–19.7) | 11.11   | (6.27–19.17)|
| Van Cutsem E [9] | Belgium      | RCT     | 999        | 566      | 59       | (9.4%)   | 25.1     | (1.1–10.9)  | 1.1     | (0.42–1.78) |
| Yokota T [71]    | Japan        | Cohort  | 319        | 214      | 15       | (6.5%)   | 40.6     | (1.43–10.2) | 4.23    | (1.76–10.2) |
| Zlobec I [13]    | Switzerland  | Cohort  | 404        | 223      | 19       | (7.9%)   | 40.6     | (1.43–10.2) | 0.53    | (0.3–1.2)   |
| Zlobec I [13]    | Switzerland  | Cohort  | 404        | 102      | 25       | (19.7%)  | 28.2     | (1.45–5.5)  | 2.82    | (1.45–5.5)  |
Table 1. Cont.

| Study          | Country       | Study design | Number of patients | Overall survival | Hazard ratio |
|---------------|--------------|--------------|--------------------|------------------|--------------|
|               |              |              | B\(\text{RAF}\text{ mutant}) |                  |              |
|               |              |              | B\(\text{RAF}\text{ WT})     |                  |              |
|               |              |              | B\(\text{RAF}\text{ subgroup})|                  |              |
|               |              |              |                     |                  |              |
|               |              |              |                     |                  |              |
|               |              |              |                     |                  |              |
|               |              |              |                     |                  |              |
| MELANOMA      |              |              |                     |                  |              |
| Kumar R [72]  | Finland      | Cohort       | 38                 | 12               | 26 (68.4%)   | 1.16         |
|               |              |              |                     |                  |              |
| Long GV [73]  | Australia    | Cohort       | 197                | 102              | 95 (48.2%)   | 1.11         |
| Si L [18]     | China        | Cohort       | 432                | 297              | 98 (24.8%)   | 1.53         |
| von Moos R [74]| Switzerland  | RCT          | 62                 | 22               | 22 (50.0%)   | 1.12         |

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Figure 2. Random effect model of Log hazard ratio (LogHR) with 95% confidence interval for studies comparing the effect of \(\text{BRAF-V600E}\) mutation on overall survival of colorectal cancer patients. A LogHR < 0 implies a survival benefit for patients with \(\text{BRAF}\) mutation. The square size indicates the power of each study in meta-analysis based on the number of patients in that study. The center of diamond shape at the lowest part indicates the combined LogHR for meta-analysis and its extremities the 95% confidence interval.

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were promising, resistance to drug treatment usually appears in almost all cases [23,35]. Typically a reactivation of MAPK pathway happens in resistant cases through other mechanisms including RAS or MEK1 mutations, COT overexpression or pathway happens in resistant cases through other mechanisms [23,35]. Typically a reactivation of MAPK inhibitor treatment is much lower than melanoma patients [40,41]. In fact, over activation and crosstalk of parallel pathways like phosphatidylinositol 3-kinase (PI3 kinase) – AKT with MAPK in colorectal cancer is playing a main role in the observed different response to BRAF inhibitor treatments in colorectal cancer. Likewise, a very recent study by Prahallad et al [42] revealed the important role of epidermal growth factor receptor (EGFR) activation in colon cancer patients as well. They showed that a feedback activation of EGFR occurs in colon cancer cells after BRAF-V600E inhibition very quickly. In fact, this feedback activation of EGFR in colon cancer cells leads to a continuous malignant cell proliferation even in the presence of BRAF-V600E inhibition. However, this mechanism would not be applicable to melanoma cells as they express a very low level of EGFR [42].

BRAF mutation in papillary thyroid cancer was reported to be a risk factor for worse survival in two studies [20,24]. Notwithstanding a notably long term follow-up of patients for 18 to 20 years in these studies from Australia and Italy, the authors either did not observe any death [24] or only one death [20] in BRAF wild-type group of patients. Authors reported only one death in a population of 64 or no death among 41 wild-type BRAF patients while Standardized Death Rate for general population in Australia was found to be 6.9 and 4.7 per 1000 standard populations for male and female respectively (http://www.abs.gov.au/ausstats/abs@.nsi/Lookup/bySubject/4125.0~Jul+2011~Main+Features~Death+rate~3210). Also, based on the report from the Centers for Disease Control and Prevention, age specific mortality rate for normal population (P=0.004) has been reported by Zlobec et al [13], while in the same study they observed a significant negative effect of BRAF mutation on patient survival for right side colon cancer (P=0.01). They did observe a significant protective effect for BRAF mutation on left side colon cancer (P=0.109). However, the negative effect of BRAF mutation on right side colon cancer patient survival was persistently significant in multivariable analysis (HR, 0.53; P=0.109). However, the negative effect of BRAF mutation on right side colon cancer patient survival was persistently significant in multivariable analysis (HR, 0.53; P=0.109). However, the negative effect of BRAF mutation on right side colon cancer patient survival was persistently significant in multivariable analysis (HR, 0.53; P=0.109). 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Table 2. Summary of studies that reported the status of BRAF mutation in papillary thyroid carcinoma with information on patient survival.

| Number of patients | Overall survival | Hazard ratio | Progression free survival | Hazard ratio |
|--------------------|------------------|--------------|----------------------------|--------------|
| Overall            | BRAF subgroup    | BRAF WT      | BRAF mutant                | BRAF mutant  |
| Abubaker J [26]    | 536              | 296          | 143                        | 153 (51.7%)  |
| Costa AM [27]      | 49               | 49           | 22                         | 27 (55%)     |
| Elisei R [20]      | 102              | 102          | 64                         | 38 (37.3%)   |
| Ito Y [25]         | 631              | 631          | 389                        | 242 (38.4%)  |
| Musholt TJ [19]    | 290              | 290          | 168                        | 122 (42%)    |
| O’Neill CJ [24]    | 104              | 101          | 41                         | 60 (59%)     |
| Stanojevic B [10]  | 266              | 182          | 84                         | 84 (31.6%)   |
| Wang W [28]        | 891              | 208          | 93                         | 115 (55.3%)  |
|                    | 177              | 67 (SBiPTC)  | 23                         | 44 (65.7%)   |
|                    | 714              | 141 (UiPTC)  | 70                         | 71 (50.4%)   |
| Xing M [76]        | 219              | 112          | 107                        | 107 (48.9%)  |

DFS, Disease free survival; OR, Odds Ratio; SBiPTC, Synchronous bilateral papillary thyroid carcinoma; UiPTC, Unilateral papillary thyroid carcinoma.

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(31 cases) and wild-type BRAF/NRAS group (80 cases). There was no data available for the effect of BRAF mutation alone on patient survival in this report. In a very similar study, Houben et al. [51] evaluated the effect of combined mutation of BRAF and NRAS mutation in 280 patients and reported a poor overall survival prognosis for metastatic samples which harbor either BRAF or NRAS mutation. However, they did not observe the same pattern in primary melanoma patients. As these two reports did not provide any information on the effect of BRAF mutation per se on patient survival we did not include them in our final meta-analysis. The inconsistency of results in these reports could be due to the fact that they combined BRAF and NRAS mutation and classified this group of patients together. In addition, Akslen et al. [14] and Chang et al. [15] reported no difference in patient survival in 69 and 68 cases respectively according to their BRAF mutation status. However, no details on patient survival have been provided in these reports. Akslen et al. [14] mostly focused on different BRAF and NRAS mutations and their combinations and possible correlation with clinicopathological characteristics. They reported that BRAF and NRAS mutations are mutually exclusive except for one case but they did not find any correlation with tumor cell proliferation, thickness or vascular invasion. Although they reported a median follow-up time of 76 months for the patients, no detailed information on mean survival time in each arm of the study was provided. There was no survival curve available in this report either. In a separate study, Chang et al. [15] observed a significant trend for liver metastasis and tendency for multiple organ metastasis in BRAF mutant group but they did not detect a significant difference in either clinicopathological characteristics or in patient survival. Basically in this study authors chose a descriptive method to explain their observation and just mentioned that they did not find any correlation between patient survival and BRAF mutation. Unfortunately, no more detailed information including mean survival time in each group of study or a survival graph has been provided by the authors. A need for a conclusive meta-analysis on the effect of BRAF mutation on melanoma patient survival has been emerged due to the controversial reports on this issue. In our meta-analysis, we combined the results of four independent studies and measured the pooled risk of BRAF mutation on melanoma patient survival. So far our report is the first study on this issue which demonstrates the correlation between BRAF mutation and poor melanoma patient survival in a reliable statistical point of view. The number of reports on BRAF mutation and colorectal cancer were enough to pool the results together and perform a meta-analysis. Therefore, our findings in the pooled data suggest that with successful BRAF inhibition we would be able to increase the survival of colorectal cancer and melanoma patients harboring BRAF mutation.

BRAF plays a very important role in cancer initiation and progression. Mutation of BRAF is detected in all stages of melanocytic lesions including nevi, primary and metastatic melanoma. It is known to be involved in the multiple stages of tumor progression such as cell proliferation [32] and invasion [6]. Interestingly, BRAF has also been shown to be involved in the progression of melanoma toward metastasis by enhancing its migration [53]. However, cancer is a complex disease with multiple markers being involved in its formation and progression. Therefore, simultaneous study of other factors involved in BRAF network is crucial for a better understanding of its role in cancer. For instance, the cooperation between BRAF mutation and PTEN loss in melanoma progression has been identified [54]. Since improving patient survival is the main goal in cancer treatment, further meta-analysis evaluation on the combination of markers involved in this critical network including RAS and PTEN with BRAF seems necessary for future planning in cancer treatment and drug development.

In summary, we used systematic review and meta-analysis approach to investigate possible association between BRAF-V600E mutation and cancer patient survival. We found that BRAF-V600E mutation increases the risk of mortality in colorectal cancer patients for more than two-fold. In addition, we revealed that BRAF-V600E mutation also significantly increases the risk of mortality in melanoma patients. This data highlights the important role of mutant BRAF in patient survival and suggest that with successful BRAF inhibition we may be able to increase the survival of colorectal cancer and melanoma patients harboring BRAF mutation.

Supporting Information

Figure S1 Complete PRISMA search for Pubmed and EMBASE 2002–2011. (DOC)

Table S1 PRISMA checklist. (DOC)

Author Contributions

Conceived and designed the experiments: GSA SMJ GL. Performed the experiments: GSA LT. Analyzed the data: GSA LT AS. Contributed reagents/materials/analysis tools: AS. Wrote the paper: GSA SMJ GL.

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